



Invasive neurostimulation in facial pain and headache syndromes

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ABSTRACT

In the mid of the 20th century various types of facial pains, not clearly originating from the teeth or the eyes, were often misdiagnosed as trigeminal neuralgia and treated with lesional techniques. Pains from the rest of the head were simply classified as “headache” and treated with the pharmaceutical means available at that time. For migraine there was often no effective therapy.

Headache is a common reasons for patients to seek medical care. Migraine is the most common form of disabling primary headache that has been estimated to be the most costly neurological disorder in the European Community at more than €27 billion per year. While considerable developments have been made in understanding and treating primary headaches there remains a group of patients with difficult to treat headache problems. Facial pain is another complex pain problem and especially severe neuropathic facial pain with considerable deafferentation has been labelled “la bête noire” of pain surgery. Many of these headache and facial pain problems are refractory to pharmacotherapy. Interventional pain management using electrical stimulation techniques can be the solution for a selected portion of these patients. In this article we describe and discuss a “treatment ladder” from minimally invasive to more interventional stimulation techniques according to the diagnosis of the pain syndrome under consideration. For each type of procedure, indications, technique and complications are discussed based on the experience of the authors and a review of the literature.

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1. Introduction

Craniofacial pain consists of a variety of conditions that needs a differentiated approach regarding pharmacological and interventional therapy. The success of any chosen therapy is essentially depending on the accurate diagnosis and thus on a preceding meticulous pain analysis. In the past, pain occurring in the distribution region of the trigeminal nerve often led to the diagnosis of classical trigeminal neuralgia (TN), whereas in some cases the diagnosis of trigeminal neuropathic pain (TNP) would have been more accurate. Actually, in some unfortunate cases the latter was the result of repeated lesional treatments for classical TN.

Different types of headaches were also misdiagnosed as TN for example hemicrania continua, trigeminal autonomic cephalalgias, cluster headache, the SUNCT syndrome and even migraine without aura. In these types of headache some of the trigeminal branches, and especially the territory of the first branch are included.

Subsequently various therapies including high doses of carbamazepine, tricyclic antidepressants, opioids, microvascular

decompression procedures and neurodestructive procedures of the trigeminal nerve where imposed, often with poor results on pain relief (Goadsby, 2005). Sweet’s well-known large scale study showed that such neurodestructive procedures did not provide any beneficial effects in these conditions and could adversely aggravate the pain symptoms – in 73% of the patients with facial neuropathic pain (Sweet, 1988).

In order to facilitate a correct diagnosis of craniofacial pain Burchiel proposed a classification scheme, based on the patients symptoms and history (Burchiel, 2003) (see Table 1). Use of the International Classification of Headache Disorders (ICHD) also can help to establish a proper diagnosis (2004).

The use of neuromodulation techniques for the management of intractable facial pain and headache was a direct spin-off of the Gate Control Theory (Melzack and Wall, 1965) although trials with sensory thalamic stimulation were initiated more than a decade earlier by Mazars in Paris (Mazars et al., 1960, 1973) – but then based on an early theory about the origin of neuropathic pain presented by Head and Thompson in the early 20th century (Head and Thompson, 1906).

The first trials with low-intensity stimulation of peripheral nerves via implanted electrodes were performed by Wall and Sweet using electrical stimulation applied to trigeminal branches on themselves (Wall and Sweet, 1967). The improvement in

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Table 1
Burchiel's classification of facial pain syndromes.

Diagnosis	History	Causes
<i>Spontaneous onset</i>		
TN, type I	>50 % paroxysmal pain	Neurovascular compression of trigeminal nerve or unknown
TN, type II	<50% paroxysmal pain	Neurovascular compression of trigeminal nerve or unknown
Symptomatic TN	TN due to multiple sclerosis	Demyelination
Atypical facial pain	Somatoform pain disorder	
<i>Peripheral trigeminal injury</i>		
TNP	Incidental non-intentional injury	ENT/oral surgery, facial trauma, stroke, etc.
TDP	Trigeminal injury from peripheral ablation	RF rhizotomy, glycerol rhizolysis, GKR, balloon compression, etc.
Postherpetic neuralgia (PHN)	Herpes zoster outbreak	Shingles involving trigeminal distribution

TN = trigeminal neuralgia, AFP = atypical facial pain, TNP = trigeminal neuropathic pain, TDP = trigeminal deafferentation pain, ENT = ear, nose and throat, RF = radiofrequency; nowadays selective thermolysis; GKR = gamma-knife radiosurgery.

anatomic knowledge and the development of appropriate equipment has resulted in the fact that neuromodulation is nowadays an integral part of the treatment algorithm for facial pain and headache syndromes.

This article aims at providing an algorithm (or treatment ladder) for the use of neuromodulation techniques for the management of facial pain and headache syndromes refractory to conventional medical treatment describing techniques starting with the most minimally invasive and superficial stimulation therapies and progressing to the more invasive approaches.

2. Methods

It is beyond the scope of this article to give a complete systematic review. In short the literature was searched for “electric stimulation or deep brain stimulation and facial pain, neuralgia, or headaches. Two reviewers (JPVB and BL) assessed the abstracts and decided on which complete publications should be extracted for further evaluation. Based on this literature review, and additional searches in selected book chapters, the indications for the different types of neuromodulation treatments are described, progressing from the least invasive to the more invasive techniques. The outcomes and complications are briefly summarised and short technical comments are supplied for each technique.

3. Invasive neurostimulation techniques for facial pain and headache syndromes

3.1. Peripheral nerve stimulation for head and facial pain (trigeminal supply area)

During the last decade a renewed interest in peripheral nerve stimulation (PNS) has arisen partly because suitable multipolar thinner and softer leads have been manufactured but also since many non-surgical colleagues (anaesthesiologists, neurologists, etc.) have adopted and extensively used neuromodulation methods preferring the more minimally invasive ones.

Actually, PNS relies on the stimulation of a field such as the subcutaneous field containing the thin often unnamed nerve branches (for the face: defined trigeminal branches).

3.1.1. Indications

PNS in the face is predominantly indicated for the management of trigeminal neuropathic pain with a clear anatomic distribution within one of the trigeminal branches without marked deafferentation (i.e. only slight hypesthesia may be present). Some of these patients can, however, experience “excitatory symptoms” such as allodynia, dysesthesia, hyperalgesia. All types of neurostimulation may be applicable even, in the presence of such symptoms, except

for Transcutaneous Electrical Nerve Stimulation (TENS) applied close to or within the painful region, which often aggravates the pain.

Trigeminal neuropathic pain may be caused by for example: trauma, major surgery, (sinus, maxillofacial, dental, aesthetic surgery) and post herpetic affections with or without major deafferentation.

3.1.2. Technique of peripheral nerve stimulation

The surgery is often performed in two stages and is similar to the approach used in spinal cord stimulation. During the first stage, an electrode lead is inserted in the vicinity of the targeted nerve branch. This is followed by trial of stimulation that lasts at least several days. If the trial is successful, the second stage of surgery involves insertion of a permanent electrode that is anchored to the fascia and tunnelled to an implantable pulse generator (IPG).

In some countries trial stimulation is performed with a potentially permanent electrode, using a temporary extension which is tunnelled to an exit through the skin.

The procedure is performed under strict surgical aseptic conditions with fluoroscopic control with heavy sedation using minimal local anaesthesia (LA) at the incision site, since widely distributed LA may disable the possibility to evoke paraesthesiae immediately after surgery. All types of electrodes can be inserted although in Sint Niklaas, a Pisces Quad Plus lead, where the electrode poles are spaced by 12 mm, allowing for stimulation of a large area, is preferred. Of course octapolar leads may also be used. In Sint Niklaas we use a custom made curved needle (Medtronic Inc., Bakken Research Centre, Maastricht, The Netherlands) preventing perforation of the skin at the tip of the needle. In most centres the surgeon himself gently bends the needle. When the needle is in place the electrode is advanced under real time fluoroscopic control until it reaches the needle tip. In the recovery room, once the patient is awake, the patient is screened and couplings tried until proper paraesthesiae have been obtained, covering the painful area. Patients are followed at regular consultations investigating pain relief. Sometimes stimulation parameters must be fine-tuned. If the trial is successful patients will be scheduled for implantation of the permanent system. Under general anaesthesia the skin is opened at the connector site and depending on the preference and physiognomy of the patient, a pocket is created at an infraclavicular, abdominal or gluteal site. The lead is connected to the battery (IPG: “Internal Pulse Generator”) by a permanent extension wire. For the trial stimulation as well as for the permanent implant antibiotic prophylaxis is given according to the local routines.

In Fig. 1 a case of neuropathic pain in the infraorbital and maxillary distribution of the right trigeminal nerve occurring after facial trauma is shown. Two quadripolar leads are implanted as seen on the radiograph.



Fig. 1. A case of posttraumatic nerve VII neuropathy treated by subcutaneous/peripheral nerve branch stimulation. Here X-rays of the head with Quad Plus (Medtronic Inc.) leads targeting the right infraorbital and maxillary branches are shown.

3.1.3. Outcomes

Only fairly small retrospective case series have been collected for PNS and as yet no randomization seem to have been performed.

In a review of prospectively collected data in 30 patients treated with PNS for craniofacial pain, stimulation was performed supra-orbitally in 7 patients, infra-orbitally in 6, and occipitally in 21. More than one nerve was stimulated in 19 patients. After the trial 22 patients were permanently implanted. After a mean follow-up duration of 35 months, the device was removed in 2 patients because of pain improvement and the device was removed in another 3 patients due to loss of effectiveness ($n = 2$) and infection ($n = 1$). Two patients experienced partial pain relief and 13 complete pain relief (Slavin, 2008).

A retrospective chart review of 10 patients treated with PNS for the management of post traumatic or post herpetic trigeminal neuropathic pain with a mean follow-up of 26.6 months showed >50% pain reduction in 70% of the patients. There was also a 70% reduction in medication use (Johnson and Burchiel, 2004).

In a series of 8 patients who underwent trial stimulation, 7 were permanently implanted because they experienced >50% pain reduction. After 1 year the electrode was explanted in one patient because of gradual loss of effect and overall improvement of pain. Another patient was re-operated because of skin erosion over the electrode. At long term follow-up (mean 27.5 months) the remaining 6 patients experienced a mean pain relief of 74% (Slavin and Wess, 2005).

Magis and Schoenen (2011a) published a detailed review of the effect of PNS and occipital nerve stimulation (ONS) for the treatment of drug-resistant chronic cluster headache.

3.1.4. Complications

The most common complication is dislocation of the lead. Erosion of the lead through the skin can occur if the lead is placed too superficially. Pain accompanying stimulation may occur if the lead is positioned too deeply or too close to a major nerve branch.

3.2. Occipital nerve stimulation

3.2.1. Indications

Occipital nerve (field) stimulation (ONS), originally launched for occipital neuralgia has recently also been successfully applied for the management of intractable headaches especially cluster headache, hemicrania continua, migraine without aura and

headache due to probable irritation of cranial nerves or cervical roots (Schoenen et al., 2010).

This technique does not only stimulate the major and minor occipital nerves but also the trigeminal – cervical complex is indirectly activated (Fig. 2). This is probably the reason why it is possible to treat different kind of headaches with this technique (Matharu et al., 2004). A Positron Emission Tomography (PET) study showed significant changes in regional cerebral blood flow that correlated to pain scores and to stimulation induced paraesthesia's.

The technique was first described by Weiner and Reed a decade ago (Weiner and Reed, 1999) and patients were considered suffering from occipital neuralgia. However, a later clinical review and PET assessment of this patient cohort showed that most of them actually had chronic migraine and one had hemicrania continua (Matharu et al., 2004).

3.2.2. Technique

The technique as initially described by Weiner and Reed that utilised a lateral approach, has been modified in order to reduce the dislocation rate. The ONS procedure is now performed under general anaesthesia or heavy sedation, since adequate LA may

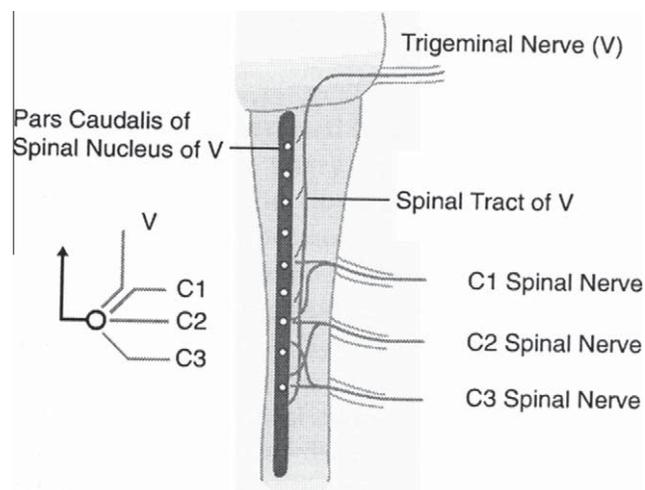


Fig. 2. The trigemino-cervical complex illustrating the complex relations between the main trigeminal nuclei, the spinal nucleus of nervus V (pars caudalis) and the upper cervical nerve roots.

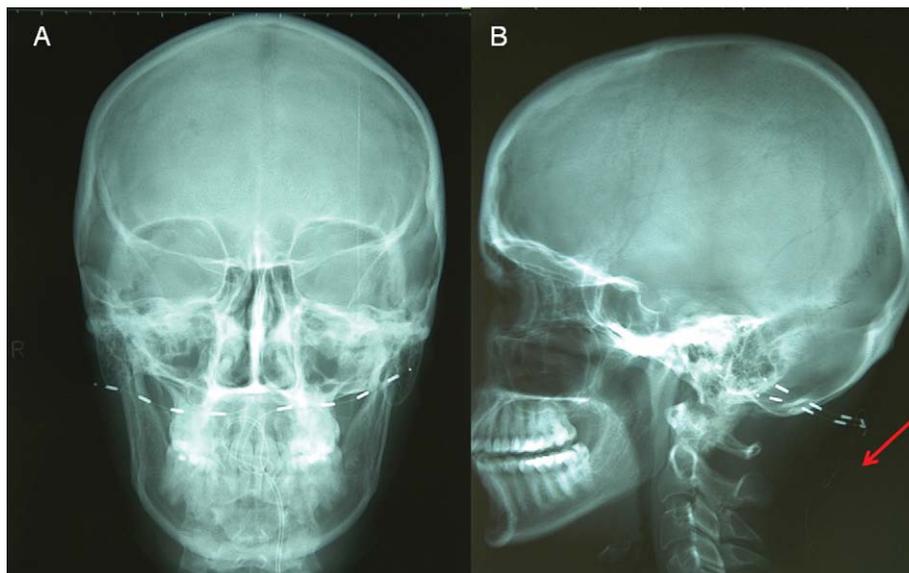


Fig. 3. (A) X-ray showing two quadripolar leads placed with a midline approach for bilateral occipital nerve stimulation. The leads are placed between the occiput and the mastoid process. In (B) the red arrow indicates the loops created to relieve strain on the system and counteract later dislocation of the leads.

complicate the later test stimulation, with the patient in the prone position and the head in a horseshoe headrest. A midline incision is made close to the occiput, where there is more fat tissue that affords a subcutaneous pocket substantial enough for adequate fixation of the lead and leaving a loop. A curved needle gently bent by the surgeon or custom made (Medtronic Inc., Bakken Research Centre, Maastricht, The Netherlands) is advanced from the occiput midline towards the mastoid process in the subcutaneous fat, crossing the greater and minor occipital nerves. Both Quad plus (Medtronic Inc) leads and octapolar leads have been used. The lead must be positioned in the subcutaneous fat tissue not too close to muscle tissue or to the nerve thus preventing from painful paraesthesia's, and also not too superficial to decrease the risk for erosion. The position of the lead is checked with fluoroscopy after the needle is pulled out. One or two anchors should be applied here to ensure that the lead(s) stay in place and after the fixation a small loop is created. An intermediate incision is made in the suprascapular area, again creating a pocket, and here a second loop is left behind. A third incision is made parallel to the spine at the high thoracic level to bury the connection between the lead and the temporary extension. The placement of the leads and the loops necessary to avoid later displacement are shown on the X-ray in Fig. 3. The connection is also fixated to the underlying tissue. The temporary extension is tunnelled laterally over the thoracic wall. After a successful trial period of at least 1 month, a pocket is created in the abdominal or gluteal area for the IPC, a new extension is tunnelled towards the connector and the new connector is secured to the underlying fascia. Stimulation parameters, including frequency, pulse width and voltage, are adjusted so that the patient experiences mild paraesthesiae in the stimulated area.

Patients must be prepared for a prolonged trial considering that some of them have additionally medication overuse headache. Medication should be tapered off gradually before the effect of the ONS per se can be evaluated.

3.2.3. Outcomes

The effect of ONS can be derived from the largest series of patients treated in one centre with this type of stimulation (Paemeleire et al., 2010).

Forty-four patients were consecutively treated with ONS for medically refractory headache.

Retrospectively these patients were reviewed by an independent third party experienced headache specialist. The best results were observed for the diagnoses ICHD 13-12: headache of neuro-pathic origin – constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions, and the second best responders suffered from migraine without aura (ICHD 1.1) while medication overuse causing headache was a bad prognostic factor.

Magis et al. (2007) found in a prospective observational study of 8 patients with refractory cluster headache that the intensity of the attacks tended to decrease earlier than the frequency. This group attributes the delay in onset of effect to slow neuromodulatory processes at the level of upper brain stem or diencephalic centres.

In a recently published randomized controlled trial, the effect of adjustable ONS was compared with preset (fixed current parameters) ONS and medical management of chronic migraine. At 3 months follow-up 39% of the patients in the group with adjustable ONS experienced >50% reduction in number of headache days a month or at least 3 points reduction in overall pain intensity as compared to baseline level. Only 6% of the patients in “the preset” ONS group and none in the medical management group reached this endpoint (Saper et al., 2011).

The beneficial effects of ONS in selected headache syndromes has been described in several review articles (Goadsby et al., 2008; Magis and Schoenen, 2008, 2011b; Trentman et al., 2011).

3.2.4. Complications

Complications of ONS are mainly due to lead dislocation, fracture or other kinds of malfunctioning mainly of the lead, connector or extension parts of the system. A few cases of skin erosion over the lead have been reported. The reported cases of infection could be treated with a short antibiotic course if they were superficial. If the infection had, however, reached the implant it was necessary to remove the whole or parts of the system.

3.3. Spinal cord stimulation

3.3.1. Indications

From the work of Barolat et al. (1993) and He et al. (1994) we know that spinal cord stimulation (SCS) is not effective in painful conditions above the C2 area since it is difficult to generate

paraesthesia properly projected to the head and neck. However, with a special approach to the C1–C2 area is the technique has been utilised in a limited number of patients with neuropathic pain covering the lower part of the face and the neck.

3.3.2. Technique

With a laterally positioned lead at the C1–C2 level, it is possible to activate the spinal trigeminal nucleus and tract which extends down to the C2-level. Even if the nucleus caudalis is considered to a large part to subserve nociception, paraesthesiae can be generated by stimulation at this level covering the face up to the mid-cheek level. A lateral X-ray of a plate lead positioned as described above is presented in Fig. 4.

High cervical stimulation has a limited applicability for head and facial pain. If it is chosen it will demand a more invasive approach where a plate electrode is implanted over C1–C2 spinal cord segment, laterally, after a partial laminectomy. This results in coverage of the lower part of the face and neck with paraesthesia.

3.3.3. Outcomes

There are but a few case series and single cases in the literature (e.g. (Afshar and Watkins, 1985)) and at Karolinska this approach was used in selected cases during the 80s and early 90s. Even lead placements at lower levels has, in single cases, relieved facial symptoms probably referred to the lower face from the chest. This may be explained by the cardiac ischaemia that in some cases only causes mandibular pain, as described also in multiple single case reports in the literature (Neuman et al., 2011). The long-term outcome of stimulation applied at the cervico-medullary junction was at best partial and today probably stimulation of superficial branches would be a better choice. In cases of combined neck and face pains however the approach still might be considered.

In a recent review of 35 cases, probably the largest material available today (Tomycz et al., 2011), the effect of implantation of plate leads at the cervico-medullary junction level between 1990 and 2009 was examined in the 25 cases available for follow-up. Actually, 16 patients received permanent implants after a successful trial (64%) while nine patients (36%) failed to obtain enough pain relief in the trial. The pain ratings on a VAS-like scale fell from 9.6 before the implant to an average of 4.8 at the follow-up, in average 53 months after implant. The best results were obtained in patients classified as suffering from trigeminal neuro-

pathic pain, trigeminal deafferentation pain or post-herpetic facial neuralgia while occipital neuralgia cases often failed.

Furthermore, unpublished data on a few cases have shown effect of high cervical stimulation on chronic cluster headache (J.-P. Van Buyten unpublished observations).

It is not unexpected that high cervical SCS would impact on autonomic functions including vascular flow in the head since a wealth of experimental animal studies and human observations has shown alterations in cerebral blood flow with SCS applied at C3 or higher levels (Visocchi, 2006).

3.3.4. Complications

Test stimulation can be performed with a compact catheter type lead placed far lateral in the upper limit of the epidural space at the C1–C2 region but with this percutaneous test implant there is usually only a partial coverage of the painful region – but few side effects. For the implantation of a plate lead on the C1–C2 level under the arcs of C1–C2 the complication rate is similar to other approaches in this region. The overall risks with SCS are well documented (Cameron, 2004).

3.4. Gasserian ganglion stimulation

3.4.1. Indications

Stimulation of the Gasserian ganglion and retroganglionic rootlets can be considered for the management of painful trigeminal neuropathy in one or several branches of the trigeminal nerve with minimal deafferentation, refractory to conventional pharmacological management and more PNS procedures.

3.4.2. Technique

This slightly more invasive strategy for the activation of large diameter fibres in the trigeminal system, consisting of stimulation of the trigeminal ganglion per se and its retroganglionic rootlets, was first reported in the late 70s and was further developed during the 80s (Steude, 1978; Meyerson and Håkanson, 1986; Holsheimer, 2001; Mehrkens and Steude, 2007). Trial stimulation was usually performed with custom made electrodes and the permanent stimulation of the Gasserian ganglion was initially performed with a bipolar plate lead (Meyerson and Håkanson, 1986). Several attempts have been made to manufacture the ideal percutaneous lead for Gasserian ganglion stimulation, e.g. the Medtronic Quinta Lead. The main problem still remains dislocation since the anchoring point in the cheek is not stable. Recently a new custom made lead has been developed with tines (Fig. 5). The electrode can be placed under fluoroscopic guidance or more recently with electromagnetic neuronavigation. The latter is Computed Tomography (CT)-based and the electrode tip is tracked in a 3-dimensional view (Van Buyten et al., 2009). Tunnelling can be performed as demonstrated in Fig. 6.

A trial period of at least 4 weeks is demanded with an externalised electrode. In preparation of the intervention a three dimensional (3D) representation of the patient's head is constructed based on three dimensional computed tomography (3D-CT) scan. This representation will allow intraoperative electromagnetic guidance by a neuronavigational system (*Medtronic 3D Stealth System*) as an aid for the needle insertion into the foramen ovale (Sint Niklaas procedure).

In the operation room the patient is placed in supine position on a carbon table. After installing standard monitoring, sedation is given using propofol. The O-arm (intraoperative CT-scanner) is placed around the head of the patient, which allows fluoroscopic and CT-imaging of the localisation of the electrode and 3D-reconstruction if needed. Based on the 3D-images entry and target point are set and a virtual track is proposed in axonal, coronal and sagittal view. Local anaesthetic is injected in the entry zone of the

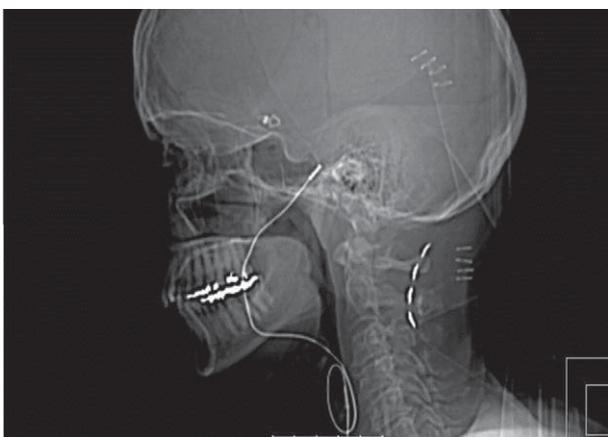


Fig. 4. A case with severe neuropathic pain in the territory of the inferior alveolar nerve (Trig. V3) after dental surgery. First, a high cervical lead (Medtronic Resume®) was applied for stimulation of the trigeminal spinal nucleus and tract at the C1–C2 level, and in addition, here a DBS lead (Medtronic model 3389) was used as a trial electrode for retrogasserian rootlet stimulation).

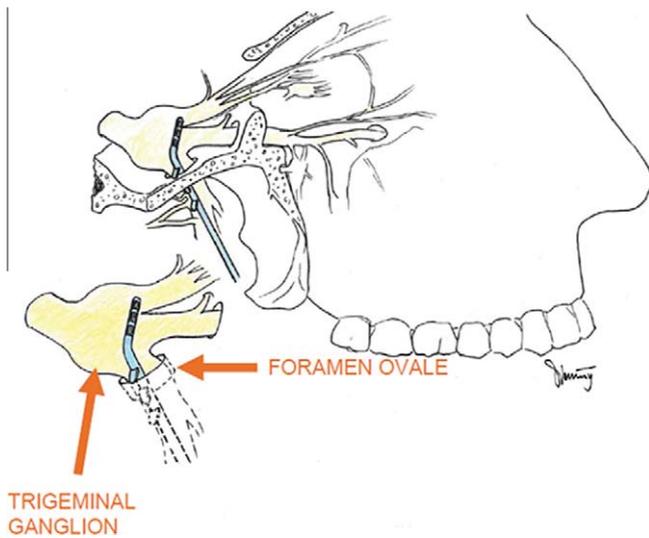


Fig. 5. Schematic drawing illustrating the approach to the trigeminal ganglion and rootlets via the foramen ovale using a recently designed curved Medtronic lead with axial tines to counteract dislocation.



Fig. 6. Schematic drawing demonstrating one variant (JBVB) of tunnelling the lead from the cheek to the extension and further to the pocket housing the IPG below the clavicle.

cheek. A small incision is made lateral to the labial commissura and a 14G non-cutting needle is inserted. The needle is guided by 3D real-time tip tracked electromagnetic aid into the foramen ovale but not through the ganglion itself. Under continuous fluoroscopy the electrode is inserted until the tip has reached the clivus. At this moment the patient is awakened and test-stimulation is performed with lead retraction until paraesthesia is evoked in the area of the pain. The needle is withdrawn under continuous fluoroscopy to assure maintenance of the electrode in the correct position and a first suture is placed subcutaneously on the entrance of the electrode using a Mercilène 4.0 suture. In Sint Niklaas no anchor is used; but at Karolinska a cut-down silicone anchor is used. The patient is then sedated again and the electrode is tunneled subcutaneously in between the maxillar-mandibular joint. A second suture is placed pre-auricular. At Sint Niklaas we chose to go to the retro-auricular region to prevent traction on the lead

by movement of the neck and jaw (Fig. 6) the Karolinska team tunnels below the ear. Finally the electrode is left subclavicular where, after positive trial, a Medtronic Itriel III-battery is implanted. Skull-base X-ray and/or CT scan confirm and document the correct positioning of the electrode (cfr. also Fig. 4 which shows off label use of a Deep Brain stimulation (DBS) lead as a trial Gasserian electrode).

3.4.3. Outcomes

Mehrkens and Steude (2007) first used floating electrodes inserted between C1 and C2 and guided under fluoroscopic control to the other side, through the foramen magnum and with the tip finally placed in the region of the cerebellopontine angle. Meyerson and Håkansson (1980) used bipolar stimulation by suturing a bipolar plate electrode directly onto the dura overlying the trigeminal ganglion. They report good pain relief in 11 out of the 14 patients who received permanent implant at a mean follow-up period of 4 years. Lazorthes et al. (1987) reported that out of 21 patients who received a trial stimulation, 5 were permanently implanted at 2 years follow-up 3 patients still experience excellent analgesic action. In another trial, 2 years after permanent implantation in 23 patients, 12 patients had good to excellent pain relief (Young, 1995). A retrospective analysis of the effect of electrical stimulation of the Gasserian ganglion in 33 patients with intractable facial pain due to peripheral damage to the trigeminal nerve ($n = 22$), central stroke damage ($n = 7$), post herpetic neuralgia ($n = 4$) and unclassifiable cause ($n = 1$), shows that 19 patients received permanent implantation. The success rate at a mean follow-up period of 22.5 months in patients with facial pain due to central damage was the highest (71%) which is surprising. Twenty-three percent of the patients with peripheral pain had successful treatment but none of the patients with post herpetic neuralgia (Taub et al., 1997). In a prospective study with 12 months follow-up 10 patients received trial stimulation and 8 had permanent implantation. After 1 year 2 patients were explanted, 1 was lost to follow up and 3 still experienced satisfactory pain relief (Machado et al., 2007). The largest series reported in a review encompasses 321 patients who received trial stimulation. Long-term follow-up data of 5 years were available in 235 patients. Fifty-two percent of them reported a minimum pain reduction of 50% (Mehrkens and Steude, 2007).

3.4.4. Complications

The shape and size of the electrode has changed over time. With the small diameter electrode (0.7 mm) no dysesthesia was reported but the electrode dislocated in 10% of the cases. The 0.9 mm diameter electrode did not dislocate in the series of Mehrkens and Steude (2007) but dysesthesia occurred in 18% of the cases. Severe infections were not reported, though local uncomplicated infections may occur.

With the newer technique and recently designed leads, certainly – if inserted with EM neuronavigation guidance – the risk for complications is minimal. Most centres, however, still use C-arm fluoroscopy intra-operatively and in experienced hands this procedure seems to be safe as well. Care should, however, be taken to control the coagulation preoperatively.

3.5. Deep brain stimulation

3.5.1. Indications

In spite of having been in clinical use for more than four decades, deep brain stimulation (DBS) can certainly not be regarded as an established, routine treatment modality. Therefore, it should be practiced only in centres with extensive experience of dealing with difficult pain problem and with a thorough knowledge of stereotactic procedures. In fact the permission to use DBS for pain has recently been withdrawn by the Food and Drug Administration

(FDA) and this treatment can by now only be used on an “off label” basis in the USA.

The main indications for DBS today for the face and head region are severe deafferentation pain in the face (facial anaesthesia dolorosa) targeting the ventral ventro-postero-medial (VPM) part of the sensory thalamic nucleus contralaterally to the painful condition and more recently also therapy resistant cluster headache aiming at the ipsilateral postero-medial hypothalamic area. This latter approach should be considered when an ONS trial has failed for at least 6 months (Linderoth and Meyerson, in press).

The periventricular gray area (PVG) as a target for DBS is rarely used in facial pain and headache as the indication for this target area is mainly nociceptive or mixed pain conditions.

3.5.2. Technique

The lead implantation itself is always performed under LA to enable intraoperative stimulation with verbal reports from the patient. Nowadays stereotactic magnetic resonance imaging (MRI), sometimes with image fusion with CT, is usually utilised for target calculation. The two classical targets the sensory thalamus (STh) (the ventro-postero-medial nuclei (VPM) and PVG are indicated in the anatomical map in Fig. 7. After test stimulation with a stiff semi-micro electrode in order to ascertain paraesthesia in the painful region, a permanent electrode is inserted to the target region and fixed to the calvarium. The technique differs between centres. Sometimes microelectrodes are used both for recording along the trajectories and for stimulation at the target site. Usually a period of trial stimulation via a percutaneous extension follows and may last for several weeks before the final implantation of the subcutaneous stimulator is undertaken (Tronnier, 2003; Wallace et al., 2004). Illustrations of preoperative planning and postop X-ray are found in Fig. 8.

There are several reasons why trial stimulation should be performed for a period of at least 1–2 weeks. First, one has to ascertain that the electrode is correctly placed as evidenced by the presence and distribution of paraesthesia in case of sensory thalamic stimulation and sometimes sensations of warmth and ocular movement, such as diplopia and even anxiety reactions at higher intensity of stimulation in the PVG target may occur. Second, a few patients

perceive the stimulation-induced paraesthesia as unpleasant or even painful. Third, the evaluation of the desired pain relieving effect is of course necessary for the decision whether to proceed to permanent implantation or not. In our experience the presence of a post-stimulatory pain relieving effect lasting for at least one hour after stimulation has been turned off is suggestive of a true suppression of the pain rather than being the result of placebo. It is therefore important to record in detail the time course of the stimulation effect. Fourth, different couplings of the stimulating poles should be tried in order to find the optimal combination. It should be noted that stimulation of the sensory thalamus should be applied with an intensity just supra threshold for evoking paraesthesia in the painful area. In the PVG target, pain relief may be obtained also with stimulus intensity sub threshold to any subjective sensations. This gives the opportunity, in the latter target, to apply a double-blind evaluation protocol during the trial period.

3.5.3. Stimulation regimens

As a rule, stimulation of the sensory thalamus must be continued for 15–30 min in order to obtain pain relief. In general, the post-stimulatory effect lasts for several hours and in exceptional cases it may persist for a considerably longer period of time. The patient should be allowed to choose the frequency, which is perceived as the most comfortable (generally 40–70 Hz). It should be noted that the pulse duration may be critical for the paraesthesia distribution and extension. Although it is a well-known phenomenon that the pain relieving effect of sensory thalamic stimulation often tends to fade during the course of the first year, there is no evidence that there is a development of “tolerance” or fatigue, which could be counteracted by restricting the usage of the stimulator.

In the PVG region, the common stimulation frequency is often around 30 Hz and the pulse duration 0.2 ms. In this target there is at least some rationale for suspecting development of “tolerance”, and for that reason the patients are instructed not to stimulate themselves for longer than 20–25 min at one time and, if possible, not more than three or four times per 24 h.

For the subthalamic target used in cluster headache most centres have used the original coordinates of Franzini et al. (2003)

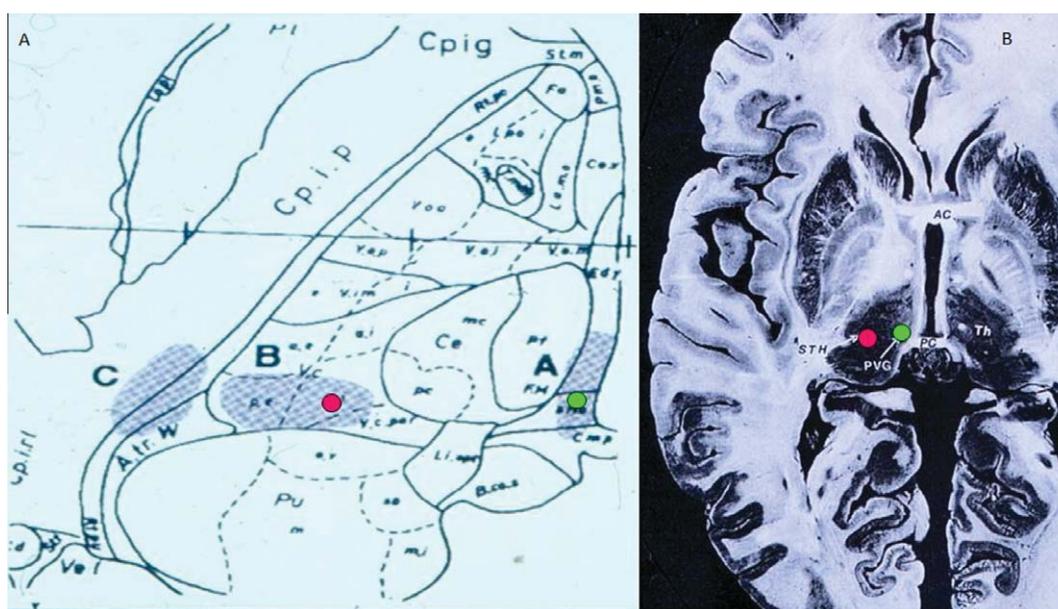


Fig. 7. A. Approximate location of the periventricular grey matter (PVG) (green dot) and the sensory thalamic nuclei VPM/VPL (VPM marked by red dot). Horizontal section 2 mm above the intercommissural plane. (B) The approximate locations of the same targets areas in a corresponding axial slice of a brain. Adapted from Meyerson and Linderoth (2001).

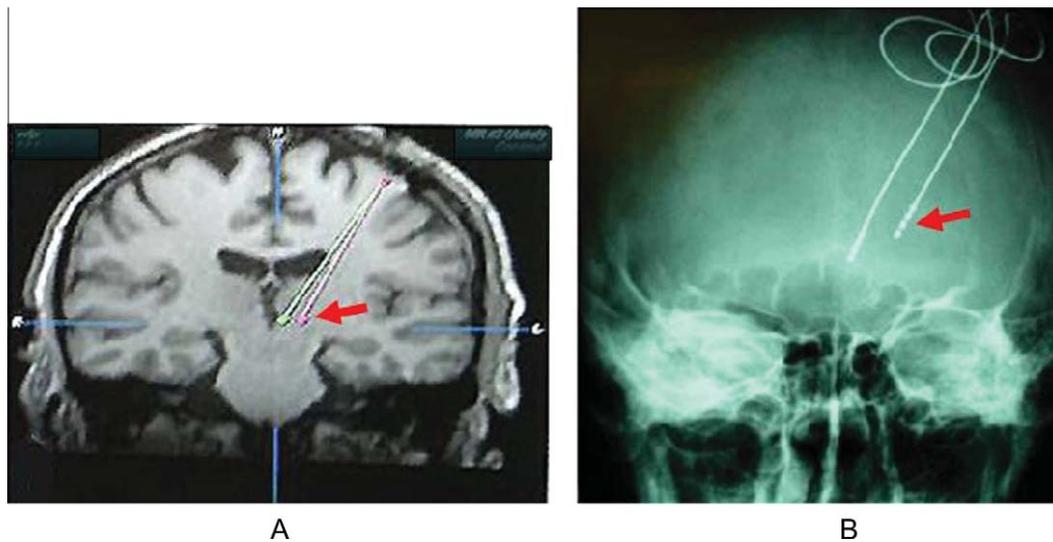


Fig. 8. (A) Preoperative console planning (coronary view) for electrode implants in the sensory thalamus (VPM) and PVG. (B) Frontal radiograph showing two stimulating electrodes implanted in the sensory thalamus and the periventricular gray matter (X-ray; Courtesy of Prof. Tipu Aziz). VPM lead indicated by black arrows. Adapted from Linderoth and Meyerson (in press).

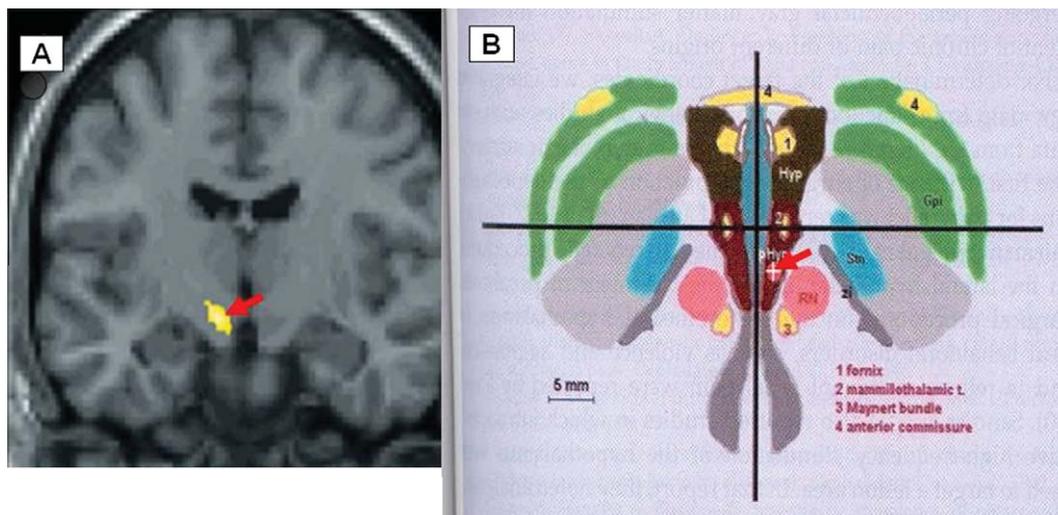


Fig. 9. Target area in the hypothalamus for DBS therapy of severe cluster headache ipsilateral to the painful side as illustrated by (A) a PET study by May et al. (1999) and in (B) a schematic drawing by the Milan group (Franzini, Leone et al. 2001–2011) indicating the target point in the postero-medial hypothalamus (red arrows point to the region of interest). Adapted from Goadsby (2005).

although the Milan group have reported similar outcomes after adjustment of the coordinates (Broggi et al., 2007). The original target is illustrated in Fig. 9 with Fig. 10 showing a target planning coronal MRI (A) and in (B) a postoperative CT (coronal projection).

3.5.4. Outcomes

The effect of DBS has been reviewed and summarised in several publications where facial pain and other pain syndromes have been mixed (Kumar et al., 1997; Tronnier, 2003; Wallace et al., 2004; Bittar et al., 2005; Levy et al., 2010). Levy (2003) performed a thorough meta-analysis of all studies including more than 15 patients. In 13 studies, comprising 1114 patients, the favourable long-term results varied between 19% and 79%. The results of several of the major DBS studies with long term follow-up clearly show that the outcome is more favourable in patients with nociceptive than neuropathic forms of pain. Young and Rinaldi (1997)

report 70 and 50% success for the two types of pain, respectively. According to the meta-analysis referred to above (Levy, 2003) it is apparent that PVG stimulation may be effective also for neuropathic pain, and in fact no less than 23% of those having long-term success had been treated with stimulation in that target. On the other hand, sensory thalamic stimulation seems to be completely ineffective for nociceptive forms of pain.

A meta-analysis of the relevant recent literature (up to 2003) showed that PVG stimulation provided good or excellent results in 79% of the patients while sensory thalamic stimulation was less efficacious (58%) (Bittar et al., 2005). The overall lower success rate reported with sensory thalamic stimulation is partly due to the fact that central pain responds rarely while a better outcome has been reported with neuropathic pain of peripheral origin (31% vs. 51%). However, as pointed out by Wallace et al. (2004) it is well known that the efficacy of sensory thalamic stimulation, in particular,

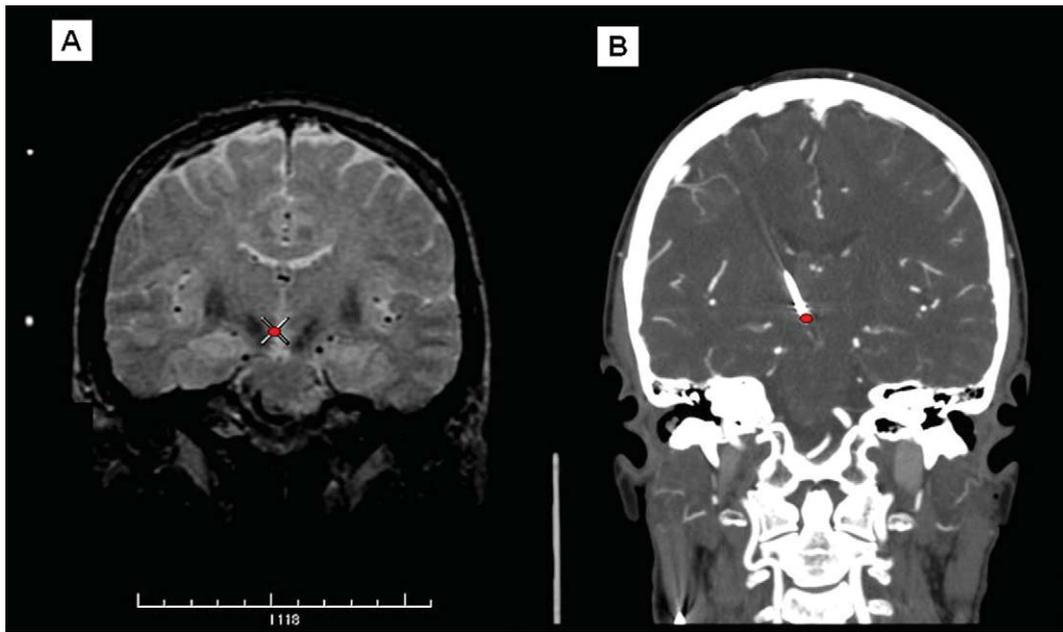


Fig. 10. Target planning based on preoperative stereotactic MRI (A) and a postoperative CT (B) demonstrating the medial location of the target in the posterior hypothalamus. For this case the target was 2 mm to the right of the midline, 3 mm behind the midcommisural point and 4 mm below the intercommisural plane. The target calculations were compared with those of the Milan group and the correspondence was good. The patient experienced after some time a marked reduction in frequency of her right-sided Horton attacks. Red dot marks target (A) and distal contact in electrode artefact (B).

often fades with time and a substantial portion of the patients reported have not been followed for more than about one year. Therefore, it might well be that the documented long-term outcome is somewhat overoptimistic, which is exemplified by a study by Hamani et al. (2006). They reported that already in the first year 8 out of 13 permanently implanted patients (of 21 subjected to trial stimulation) discontinued stimulation, and only five maintained a long-term benefit.

In the few case reports on effects of VPM and PVG stimulation specifically for facial pain syndromes (Green et al., 2005; Owen et al., 2006; Thomas et al., 2009) pain relief is reported to vary between 37% and 49% of the pre-stimulatory level although Green et al. (2005) observed a pain reduction of more than 50% and that 5/7 patients in this small series were pleased with the outcome. The conclusion is that DBS directed to the sensory thalamus or the PVG may in selected cases and in experienced hands provide a safe and effective therapy for a variety of facial pains and other painful syndromes in the head (even in some cases of post-stroke facial pain (e.g. Owen et al., 2006).

3.6. Hypothalamic DBS for cluster headache

3.6.1. Brief background

Based on the PET imaging finding that attacks of headache are associated by activation of the posteromedial hypothalamus (May et al., 1998; Goadsby and May, 1999). Franzini et al. (2003) tried DBS in cases of severe Horton's syndrome and reported that stimulation applied in this region could produce an effective pain relief in this otherwise notoriously therapy resistant condition. Since then a total of some 60 cases have been documented and in about 60% of them the stimulation has been successful in preventing the painful attacks (Leone et al., 2010). The target area is illustrated in Figs. 9 and 10, the latter showing the preoperative target planning based on the stereotactic MRI and a postoperative coronal CT with a right sided lead.

3.6.2. Outcomes

However, despite the early enthusiasm for this approach more recent data from multicenter randomized and blinded trials have cast some doubt about its true place in the treatment ladder for cluster headache (Stadler et al., 2011). In the French multicentre trial (Fontaine et al., 2010) there were no significant differences in pain episodes in patients who were blinded as to whether they were given true or "placebo (off)" stimulation.

Recently one of the senior authors from the Milan group admitted that at present ONS, the first line method for the cluster headache is efficient in most (70%) of the trial cases while hypothalamic DBS is restricted to a limited number of cases (Franzini personal communication, 2011; Franzini et al., 2008).

ONS, thus, has an equal or better outcome and considering the invasiveness of hypothalamic stimulation and the higher risk of side effects this latter treatment has to be considered as a last resort. Actually, it was recently reported (Franzini personal communication, 2011) that even in Milan only 6/20 of cases suffering from chronic cluster headache underwent hypothalamic DBS after a trial with ONS.

3.6.3. Complications

With normal haemostasis the risk for haemorrhage along the electrode trajectory is low and with modern techniques not expected to exceed 0.5% of the cases. Hypothalamic stimulation intraoperatively, however, can induce severe panic attacks if stimulation amplitudes are too high.

3.7. Motor cortex stimulation

3.7.1. Indications

When Tsubokawa et al. (1990) presented this new approach of motor cortex stimulation (MCS) in 1990 the main indication was central pain (post stroke pain). When this technique subsequently was applied in other centres the favourable outcome of Tsubokawa in central pain was difficult to reproduce but instead motor cortex

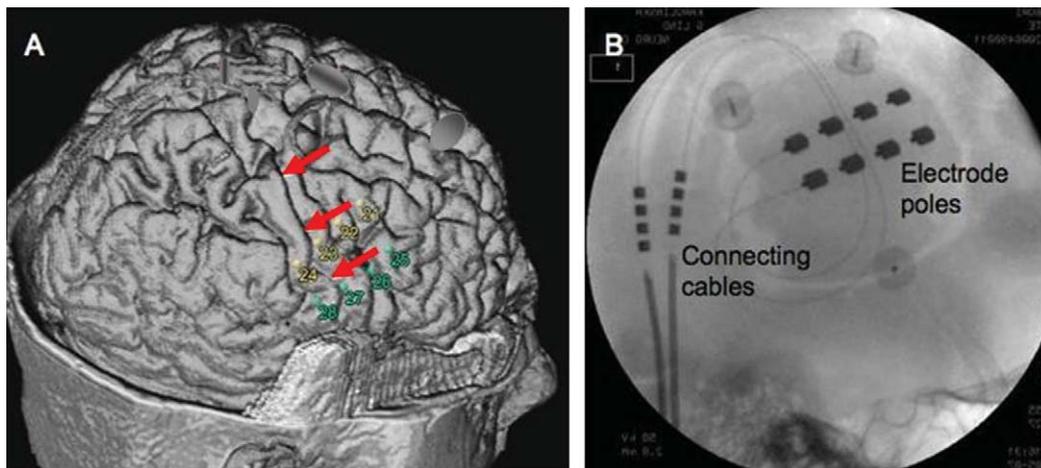


Fig. 11. (A) Intraoperative use of neuronavigation and electrophysiology to identify the optimal positions (grid poles are marked by numbers) for positioning of plate leads for motor cortex stimulation. Red arrows indicate the central sulcus as determined visually and by intraoperative neurophysiology. (B) X-ray showing two four-polar plate electrodes placed perpendicular to and crossing the targeted part of the motor cortex. Adapted from Linderoth and Meyerson (in press).

stimulation was found to be very effective for deafferentation facial pain (trigeminal neuropathy) (Meyerson et al., 1993; Meyerson and Linderoth, 2001). MCS has in recent years been adopted by several centres but still the number of patients documented in the literature is relatively small, <300 (Fontaine et al., 2009) albeit the amount of papers on MCS is increasing.

MCS has recently been tried in a variety of pain conditions but still trigeminal deafferentation pain remains the best indication.

3.7.2. Technique

Initially Tsubokawa and others used a single burr hole approach with the patients fully awake being able to report on evoked sensations, side effects etc. However neurosurgeons changed to an approach using a small craniotomy for the following reasons: better control of haemostasis, possibility to apply a multipolar plaque on the dura mater for recording of sensory evoked potentials (SEP) in order to physiologically define the location of the motor cortex. Most centres now perform the procedure under full anaesthesia with craniotomy on the side contralateral to the painful area where sensory evoked potentials are recorded and the phase reversal of the M20/P20 defines the division between the motor and sensory cortex surfaces.

Preoperatively a high quality MRI of the brain is obtained with a 3 D reconstruction of the cortical surface. During surgery this MRI is used together with a neuronavigation system for optimal placement of the craniotomy and for the visual identification of the motor cortex. If available a preoperative fMRI can be of great help to identify the proper part of the motor cortex. When a final identification has been performed with SEPs, cortical stimulation is used and motor activation within the painful body parts is recorded visually and/or with the help of electromyography (EMG). There are two options to place leads. Nowadays many centres use dual leads (Medtronic Resume[®]) which could be placed along the motor cortex or perpendicular to the motor strip. Usually trial stimulation is performed for some weeks after the implant via percutaneous wires.

Although MCS is less invasive than DBS due to the fact that the leads are placed outside the dura mater, this technique requires a large multidisciplinary team present in the operation theatre. This reduces its use to highly specialised centres. The technique is illustrated in Figs. 11 and 12 showing the intraoperative testing and the final placement of two plate leads onto the dura overlying the motor cortex.

3.7.3. Outcomes

In a recent literature review 14 MCS-studies, selected from 244 publications (1991–2006), were analysed (Fontaine et al., 2009). A good response was reported in 54% of 117 patients with central pain and in 65% of patients with facial pain due to trigeminal neuropathy. A study of Rasche et al. (2006) reported on long-term outcome (mean 3.6 years): 50% of cases with central pain and 43% with trigeminal neuropathy retained a good effect. Somewhat better results have been reported in a study by Nguyen et al. (1999) where 10 out of 12 patients with such pain and with a mean follow-up of 27 months experienced substantial relief. Recently, Nguyen (J.-P. Nguyen personal communication, 2011) summarised the results from his centre thus; for severe trigeminal neuropathic pain about 76% of patients obtained long-term satisfactory/good pain relief.

The largest series of patients with central pain (31 patients, including some cases with spinal pain and root avulsion pain) with a mean follow-up of four years was reported by Nuti et al. (2005). Excellent to good pain relief was achieved in 52% of the patients, though 70% of all cases declared themselves to be satisfied and favourable to a re-intervention given the same outcome.

A characteristic feature of MCS is that the stimulation is not accompanied by any subjective sensations, and this enables double blind study designs. In fact, already in the first report on MCS for

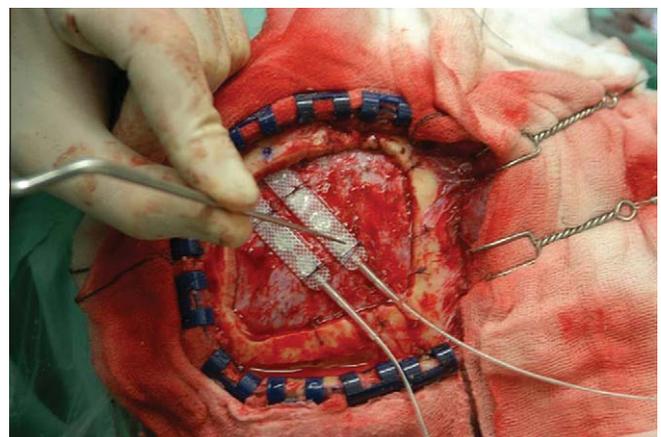


Fig. 12. Photograph showing two leads (Resume[®] Medtronic Inc.) sutured to the dura overlying the motor cortex.

trigeminal neuropathy this approach was applied in one of the early patients (Meyerson et al., 1993). Recently, a few blinded randomized controlled studies have been published and they confirm the beneficial results that have previously been reported by numerous open label studies (Nguyen et al., 2008; Velasco et al., 2008; Lefaucheur et al., 2009).

A majority of patients with central pain, as well as trigeminal neuropathy, present also with various forms of evoked pain: allodynia and dysesthesia. In several studies it has been reported that the evoked pain components may also be controlled by MCS (Velasco et al., 2009).

Furthermore MCS has been tried for a number of other forms of severe neuropathic pain (Lefaucheur et al., 2009; Prévinaire et al., 2009). In about half of the patients the treatment has been useful.

3.7.4. Complications and side effects

No serious complications associated with the implantation procedure or long-term application of MCS have been reported in the literature. Epidural haematomas were initially reported to occur in a few patients. The use of a generous bone flap for electrode implantation instead of the original single burr hole approach enables a more rigorous control of haemostasis. Several cases with stimulation-induced local pain at the site of the electrode have been described. This pain originates from the dura and it may be so troublesome that it necessitates a craniotomy and denervation of the dura by cutting and re-suturing the part underlying the electrode.

As with all implanted materials there is an increased risk of infections, which have been reported to occur in about 5%. Hardware related problems (about 5%) have also been reported to be relatively common.

In the trial stimulation phase, when different stimulation parameters are explored, stimulation-induced fits are relatively common, especially with aggressive reprogramming (Henderson et al., 2004). Of course, there is a fear that long-term stimulation could have a kindling-like effect resulting in a state of manifest epilepsy. No such case has been documented in the literature but the Karolinska group have had experience of one patient who after two years of MCS treatment developed intractable epilepsy of the Jacksonian type still persisting after many years. However, it is not proven beyond doubt that the epilepsy was the result of MCS *per se* since it started shortly after an intervention for denervation of the dura because of unbearable local pain. The fits necessitated a re-exploration, which revealed a thin subdural clot measuring approximately 4×4 cm. At inspection no cortical lesion could be detected and the cortical surface had a normal appearance. The electrode was of course removed. Subsequent MRI and PET examinations have failed to reveal any local pathology, which could account for the persisting, daily motor fits. Since there is thus no definite proof that the stimulation itself was the principal cause for the development of epilepsy in this case, it has previously not been reported.

4. Discussion

Until recently many cases of facial neuropathic pain and refractory headaches have been misdiagnosed and undertreated because no suitable methods for treatment were available except for lesional techniques indicated only as a last resort in desperate cases and in cancer pain patients with limited expected survival time. Only with the advent of neuromodulation techniques during the last decades have more lenient methods appeared as strong alternatives to the previously used neurodestructive techniques and long-term pharmacological treatment with their ensuing side effects. In this review we have tried to present a treatment ladder

from minimally invasive to more invasive neurostimulation techniques for the treatment of these conditions. Also side-effects and problems have been reviewed and the present place for each approach has been indicated. As an example a therapeutic ladder for a case of neuropathic facial pain is demonstrated in Fig. 13 which shows sites where the trigeminal system can be activated from the periphery to the centre. Also MCS and high cervical SCS is illustrated in this graph. For pharmacotherapy-resistant headaches the therapeutic ladder simply recommends starting with minimally invasive PNS and, only in cases with a negative long-term trial with this approach, progress to more invasive e.g. intracranial procedures.

It should be understood from this review that the authors support the use of peripheral minimally invasive techniques in the first place. The progression to a more invasive procedure targeting intracranial structures has to be a second choice on the treatment ladder – and this seems to be valid for all the diagnoses discussed in this review. The possibility of performing randomized prospec-

Severe trigeminal neuropathy due to nerve lesion

Trials:

- 1. Peripheral nerve stimulation
- 2. Retrogasserian root fiber stim.
- 3. Sensory Thalamic stim. (VPM)
- 4. Motor Cortex stim.

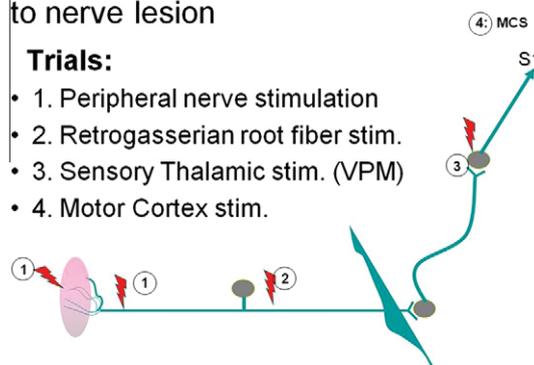


Fig. 13. Schematic figure illustrating different target points where the trigeminal system may be stimulated. If the deafferentation in part of the face is marked (as determined by sensory investigation and surface stimulation) only motor cortex stimulation or sensory thalamic (VPM; producing paraesthesiae in the pain area) stimulation could provide relief from the pain.

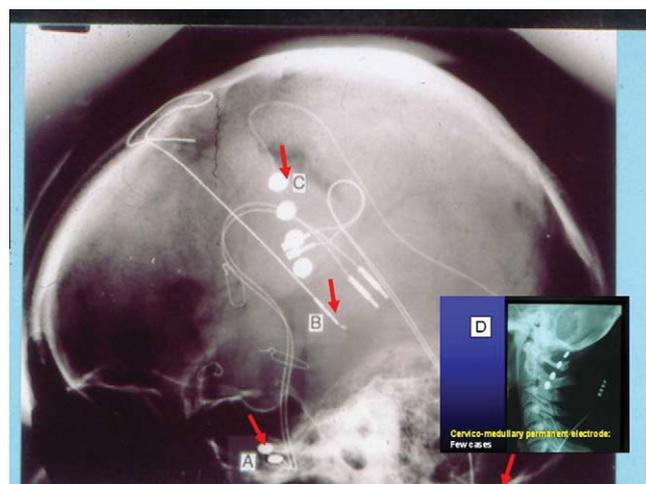


Fig. 14. Radiograph illustrating therapy trials with various types of neurostimulation applied from the early 80s into the 90ies. The patient suffered from severe deafferentation facial pain and trials were performed with Gasserian ganglion stimulation via a bipolar plate lead (A), sensory thalamic stimulation via a VPM lead (old type) (B), motor cortex stimulation via a lead along the motor strip (early burr hole approach) (C) and via a C1–C2 plate lead (Medtronic Resume[®]) placed over the spinal trigeminal nucleus and tract (inset; D)

tive blinded trial with some techniques not producing paraesthesia (e.g. MCS, PVG stimulation, hypothalamic stimulation) supplies a unique opportunity to obtain solid evidence of the efficacy of a technique and the first studies with such a design further emphasize and support the usage of peripheral approaches as far as possible.

An extremely complicated and desperate case treated many years ago is illustrated in Fig. 14. However, it must be remembered that for the paroxysmal facial pain conditions such as classical TN or TN secondary to for instance multiple sclerosis (MS) the lesional techniques are still important and in such conditions neurostimulation at present has little to offer. For the typical neuropathic facial pain conditions with or without exacerbations of extreme pain as well as for a variety of headache syndromes the use of neuromodulation methods will probably increase over the next years. The implants will probably even prove to be very economical as compared to recently developed pharmaceutical agents as seen over just a couple of years.

Conflict of interest

None of the authors have a conflict of interest.

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