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EAN guideline on trigeminal neuralgia.

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SUMMARY

Background: Trigeminal neuralgia (TN) is an extremely painful condition, which can be difficult to diagnose and treat. In Europe, TN-patients are managed by many different specialities. Therefore, there is a great need for comprehensive European guidelines for management of TN. The European Academy of Neurology asked an expert panel to develop recommendations for a series of questions that are essential for daily clinical management of patients with TN.

Methods: We performed a systematic review of the literature and developed recommendations based on GRADE, where feasible, if not a good practice statement was given.

Results: We recommend the use of the most recent classification system, which diagnoses TN as primary TN, either classical or idiopathic depending on the degree of neurovascular contact, or as secondary TN caused by pathology other than neurovascular contact. An MRI, using a combination of three high-resolution sequences, should be performed as part of work up in TN patients, because no clinical characteristics can exclude secondary TN. If MRI is not possible, trigeminal reflexes can be used. Neurovascular contact plays an important role in primary TN, but demonstration of a neurovascular contact should not be used to confirm the diagnosis of TN. Rather, it may help to decide if and when a patient should be referred for microvascular decompression. In acute exacerbations of pain, intravenous infusion of fosphenytoin or lidocaine can be used. For long-term treatment we recommend carbamazepine or oxcarbazepine as drugs of first choice. Lamotrigine, gabapentin, botolinum toxin type A, pregabalin, baclofen and phenytoin may be used either alone or as add-on therapy. We recommend that patients should be offered surgery if pain is not sufficiently controlled medically or if medical treatment is poorly tolerated. Microvascular decompression is recommended as first-line surgery in patients with classical TN. No recommendation can be given for choice between any neuroablative treatments or between them and microvascular decompression in patients with idiopathic TN. Neuroablative treatments should be the preferred choice if MRI does not demonstrate any neurovascular contact. Treatment for patients with secondary TN should in general follow the same principles as for primary TN. In addition to medical and surgical management, we recommend that patients are offered psychological and nursing support.

Conclusions: Compared with previous TN guidelines, there are important changes regarding diagnosis and imaging. These allow better characterization of patients and help in decision making regarding the planning of medical and surgical management. Recommendations on pharmacological

and surgical management have been updated. There is a great need for future research on all aspects of TN, including pathophysiology and management.

INTRODUCTION

Trigeminal neuralgia (TN) is an extremely painful disorder, which can be difficult to diagnose and treat. In Europe, TN-patients are managed by many different specialities including general practitioners, anaesthesiologists, dentists, neurologists and neurosurgeons and are only rarely concentrated in highly specialized centres. Therefore, there is a great need for comprehensive European guidelines for the management of TN.

The first guideline from the European Federation of Neurological Societies (EFNS) on TN was published in 2008 in cooperation with the American Academy of Neurology (AAN) [1]. Since then, important new knowledge has emerged regarding diagnosis, clinical characteristics and imaging, and new drugs are emerging. Moreover, the recommendations for preparation of guidelines have been updated [2], in particular the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system has been established and endorsed by the European Academy of Neurology (EAN) [2] as the method of choice to establish recommendations. The EAN therefore decided that the guideline for TN management needs revision.

One of the changes that occurred after the publication of the previous AAN-EFNS guideline is with regard to classification and terminology. In an attempt to settle the anarchic terminology and the different settings between the International Association for the Study of Pain (IASP) and the International Headache Society (IHS), a new classification laid out three aetiological categories: idiopathic TN (no neurovascular contact or neurovascular contact without morphological changes of the trigeminal root), classical TN (due to a neurovascular compression with morphological changes of the trigeminal root), and secondary TN (STN) (due to major neurological disease such as cerebellopontine angle tumours or multiple sclerosis), and two phenotypes: purely paroxysmal TN (with paroxysmal pain only) and TN with concomitant continuous pain [3]. This classification and terminology have been shared by the latest edition of the International Classification of Headache Disorders (ICHD) [4] and by the WHO's International Classification of Disease [5]. Throughout this guideline we have adopted the above aetiological and phenotypical classification. Previously classical TN included what is now both idiopathic and classical TN. In this guideline the term primary TN (PTN) is used to describe a population consisting of patients with idiopathic TN as well as patients with classical TN.

METHODS

The EAN identified an expert panel consisting of 14 members, including members within the field of neurology, pain, neurosurgery, imaging and dentistry as well as a patient representative. Ten working groups each consisting of 4-5 members were appointed and were each responsible for one clinical question.

We developed recommendations for a series of questions that are essential for the daily clinical management of patients with TN. Where possible, the Patients; Intervention; Comparison and Outcome (PICO) [2] method was used.

The first issue facing the clinician caring for a patient with TN is to establish the correct diagnosis. The diagnostic part of this guideline addresses the following questions:

1.1. Which clinical features correctly identify patients with secondary TN?

1.2. Which laboratory tests are required?

1.3. What role does neurovascular contact play in TN?

1.4. Which kind of imaging should be performed?

First line therapy of TN is pharmacological. The pharmacological treatment part of this guideline addresses the following questions:

2.1. How to manage acute exacerbations?

2.2. Which drugs have shown efficacy in TN in the long term?

Surgery should be considered if medical treatment is not effective or tolerated. The surgery therapy part of this guideline addresses the following questions:

3.1. When should surgery be offered?

3.2. Which surgical technique gives the longest pain free period with the fewest complications?

Management of secondary TN and management of TN where medical and surgical options are exhausted can be challenging. The final part of this guideline addresses the following questions:

4.1. How to manage secondary TN?

4.2. What other support can be provided for patients with TN?

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The GRADE [2] method was used to develop recommendations. Final quality of evidence was rated as high, moderate, low or very low based on study design, study limitations, inconsistency, indirectness, imprecision, publication bias, effect size, dose response and confounding. Strength (strong or weak) and direction (for or against) of recommendation were determined on the basis of balance between desirable and undesirable effects, quality of evidence, values, and preferences and costs [2].

If GRADE was not applicable, a good practice statement was given, according to the available level of evidence. The Delphi method was used to reach consensus. To keep this guideline within the allowed length and to increase clarity, we have condensed some of the chapters. The full background including references and tables has been published as supplementary material.

SEARCH STRATEGY

Papers published in peer-reviewed journals were identified using PubMed/Medline, EMBASE and Cochrane Library. Search terms depended on the specific clinical question. A total of 10 working groups were appointed to cover the clinical questions. Each working group identified the relevant search terms and performed the search. The chair for each working group was responsible for the search strategy and selection of papers. Searches were restricted to English language and time frame was since 2006 (last date of search of prior AAN-EFNS guidelines).

SECTION 1: DIAGNOSIS

Clinical question 1.1: For patients with TN which clinical features correctly identify patients with secondary TN?

Search strategy and results

We searched for papers studying the diagnostic accuracy of clinical characteristics for distinguishing primary from secondary TN. In addition to the papers included in the previous guideline [6-11], we identified two new papers [12, 13]. Involvement of the first trigeminal division and poor response to treatment were not significantly associated with secondary TN (Table 1.1). Secondary TN patients were significantly younger compared to primary TN patients. However,

there was considerable overlap in the age ranges of patients with primary TN and secondary TN. Trigeminal sensory deficits were significantly more common in patients with secondary TN. However, many patients without sensory deficits had secondary TN reflecting low sensitivity. Bilateral secondary TN was in one study very frequent in TN due to multiple sclerosis (MS) but was not seen in studies of TN due to masses. Bilateral pain is thus associated with secondary TN due to MS but most secondary TN patients have unilateral pain reflected in a low pooled sensitivity.

Clinical guide

No clinical features have a high sensitivity in identifying patients with secondary TN. Patients with secondary TN seem to be younger, more likely to have trigeminal sensory deficits and bilateral pain. However, the absence of these features does not rule out secondary TN and magnetic resonance imaging (MRI) is therefore strongly recommended as a part of early work up in TN patients.

Final recommendation

Based on low evidence, no clinical characteristics can exclude secondary TN. MRI is strongly recommended as part of work up in TN patients.

Clinical question 1.2: For patients with facial pain, which laboratory tests are required to diagnose secondary TN? Which laboratory tests distinguish primary TN from other neuropathic facial pain conditions?

Search strategy and results

We searched for papers reporting on the diagnostic accuracy of trigeminal reflex testing and evoked potentials for distinguishing secondary TN from primary TN. We also searched for papers addressing the role of laboratory tests in detecting trigeminal afferent damage in other neuropathic facial pain conditions. Eight studies reported the trigeminal reflexes findings in patients with TN [6, 14-20] (Table 1.2a). The diagnostic accuracy of trigeminal reflexes for identifying secondary TN patients was relatively high with sensitivity 59% to 100% and specificity 93% to 100%; pooled sensitivity 94%; pooled specificity 88%. Six studies reported the evoked potentials findings in patients with TN [17, 19, 21-24] (Table 1.2b). In contrast to the trigeminal reflexes, evoked

potentials may be altered even in idiopathic or classical TN. A pooled sensitivity of 84% and a pooled specificity of 52% were found.

Two studies reported trigeminal reflex and evoked potentials findings in patients with postherpetic neuralgia [25, 26]. The diagnostic accuracy of neurophysiological tests for identifying trigeminal afferent damage in the affected side was high with pooled sensitivity 100%; pooled specificity 100% and 88% respectively. One study reported masseter inhibitory reflex findings in iatrogenic damage to the mandibular nerves [27]. Specificity and sensitivity were 99% and 51% respectively. These findings indicate that masseter inhibitory reflex testing, showing an almost absolute specificity, reliably demonstrates nerve damage, whereas the relatively low sensitivity makes the finding of a normal masseter inhibitory reflex by no means sufficient to exclude nerve damage. Jääskeläinen and colleagues [28] found abnormal mental and lingual nerve blink reflexes in 38% of patients with trigeminal neuropathy due to surgical procedures. Trigeminal reflex recording is particularly helpful in rare cases of trigeminal isolated sensory neuropathy and facial-onset sensory motor neuropathy syndrome [29] that may manifest, in early stages, with unilateral paroxysmal pain.

Clinical guide

MRI is the first-choice tool for diagnosing secondary TN. If MRI is contraindicated or unavailable, testing of trigeminal reflexes is useful to distinguish secondary TN from primary TN. Trigeminal reflexes and evoked potentials are also needed to detect trigeminal afferent damage in patients with different neuropathic facial pain conditions.

Final recommendations

In cases where MRI is contraindicated or unavailable, a strong recommendation is given about the use of trigeminal reflexes to distinguish secondary TN from primary TN. For patients with TN, abnormal trigeminal nerve evoked potentials are probably associated with an increased risk of secondary TN. However, there is too much overlap in patients with primary TN and secondary TN for this predictor to be considered clinically useful. A strong recommendation is given against using evoked potentials to identify secondary TN. In patients with different neuropathic facial pain conditions, trigeminal reflexes and evoked potentials are needed to detect trigeminal afferent damage.

Clinical question 1.3: What role does neurovascular contact play in primary TN?

Search strategy and results

We searched for reports of prospective studies of broad-spectrum primary TN patients comparing the blinded symptomatic and asymptomatic side by high resolution MRI and grading the neurovascular contact (NVC) as to whether there are morphological changes of the trigeminal nerve. We defined "broad-spectrum" to be TN patients from neurological settings. We identified 3 studies fulfilling the search criteria [30-32]. All three studies were prospective cohort studies. NVC of any kind was a frequent finding on the asymptomatic side (151/175 asymptomatic nerves) (Table 1.3a), while NVC with morphological changes was a rare finding on the asymptomatic side (20/175 asymptomatic nerves). Idiopathic TN was moderately associated with an NVC without morphological changes on the symptomatic side (OR 2.3, $p = 0.008$) (Table 1.3b). Classical TN was highly associated with NVC with morphological changes on the symptomatic side (OR 13.3, $p < 0.001$).

Clinical guide

TN is associated with NVC of any kind on the symptomatic side and highly associated with NVC with morphological changes on the symptomatic side. As NVC without morphological changes is a frequent variation of normal neuroanatomy, NVC should not be used as a diagnostic tool to diagnose or exclude TN in facial pain patients. In a recent prospective study using independent assessors of outcome, it was demonstrated that patients with classical TN have a higher chance of a successful outcome after microvascular decompression (MVD) when compared to idiopathic TN patients [33]. However, a significant proportion of patients with idiopathic TN also had good pain relief after MVD [33]. Thus, it seems that an NVC without morphological changes does play a role in some idiopathic TN patients who are therefore not truly "idiopathic". In idiopathic TN, and probably also to lesser degree in classical TN, other currently unknown etiological factors probably play an important role.

Final recommendations

Based on a high quality of evidence, a strong indication is given that idiopathic TN is moderately associated with NVC without morphological changes and that classical TN is highly associated with

NVC with morphological changes. Therefore, demonstration of NVC should not be used to confirm the diagnosis of TN. Rather, it may help to decide if and when a patient should be referred for an MVD.

Clinical question 1.4: For patients with TN, which kind of imaging should be done to demonstrate neurovascular contact and rule out other causes of TN?

Search strategy and results

We searched for TN studies evaluating NVC using MRI, three-dimensional (3D) imaging, 3D T2-weighted imaging, 3D time-of-flight (TOF) magnetic resonance angiography (MRA) and 3D T1-weighted gadolinium (T1-Gad). We investigated studies using imaging protocols to facilitate the diagnosis of TN and to detect the presence of NVC in comparison to intraoperative data. The following criteria for acceptable studies were set: 1. diagnostic criteria stated; 2. a minimum of 20 patients that had undergone MVD to allow a comparison with preoperative imaging analysis; 3. MRI characteristics (machinery and sequences); 4. blinded control studies; and 5. unequivocal data of sensitivity and/or specificity for detection of NVC.

No randomised controlled trials were identified. We found 15 studies investigating the accuracy of preoperative imaging examination to predict the presence of NVC [34-48]. All studies compared the preoperative imaging analysis with surgical data. Nine studies were performed using a 1.5-Tesla (T) MR scanner [34, 36, 38, 40-43, 45, 46], six with a 3-T scanner [35, 37, 39, 44, 47, 48], five studies applied an imaging protocol with only 3D TOF-MRA [34, 37, 40, 43, 45]; five with a combination of 3D T2-weighted and 3D TOF-MRA [36, 38, 39, 42, 46]; two with a combination of 3D T2-weighted, 3D TOF-MRA and 3D T1-Gad [41, 48]; two with a combination of 3D TOF-MRA and 3D T1-Gad [35, 47]; and one study with a combination of 3D T2-weighted and 3D FLAIR [44]. The sensitivity and the specificity of imaging protocol in detecting NVC varied, respectively, from 67% to 100% and from 50% to 100%.

Clinical guide

Standard MRI can be used to exclude secondary intracranial pathology such as MS and tumours but has not proved to be sufficient to establish or exclude vessel-nerve contact. High-spatial-resolution 3D T2 sequence (driven equilibrium, DRIVE; constructive interference in steady state, CISS; fast

imaging employing stead-state, FIESTA) all allow excellent contrast between the cerebrospinal fluid (hypersignal) and neurovascular structures (hyposignal) producing high-performance cisternography [48]. The limitations are the lack of signal differentiation, not only between arteries and veins and between vessels and nerves, but also for the brain parenchyma. 3D TOF-MRA provides good visualization of the arteries in hypersignal, contrasting with the cerebrospinal fluid in hyposignal. Nerves are visible, but they are difficult to distinguish because of their intermediate signal [48]. Veins, because of their low flow, are not usually visible, especially if a band of presaturation filter is applied. 3D T1-Gad allows the visualization of nerves in intermediate signal in relation to cerebrospinal fluid and shows both arteries and veins in hypersignal [48]. Three Tesla is probably preferable over 1.5-T. Thin slices should be used. It should be described whether a vessel contact causes morphological changes of the nerve. It is recommended that the neuroradiologist is blinded to the side of pain in order to avoid bias in evaluation of NVC. If MRI is unavailable or contraindicated a computed tomography (CT) scan with contrast should be considered to rule out tumours.

Final recommendations

MRI should be performed in all patients to exclude secondary causes of TN. A combination of three high-resolution sequences - 3D T2-weighted, 3D TOF-MRA and 3D T1-Gad - aid the detection of a possible NVC. The neuroradiologist should be blinded to the side of pain. It should be described whether a vessel contact causes morphological changes of the nerve. These recommendations are based on low quality of evidence.

SECTION 2: PHARMACOLOGICAL TREATMENT

Clinical question 2.1: For patients with primary TN, which interventions are effective in the treatment of acute exacerbations of pain?

Search strategy and results

We searched for reports on the use of intravenous drugs in the emergency management of TN. We found one randomized controlled trial (RCT) on the use of intravenous lidocaine in acute exacerbation [49]. In this trial, a single dose of intravenous lidocaine (5 mg/kg over 60 minutes)

was superior in reducing pain intensity compared to placebo during the first 24 hours after the infusion. The most common side effect was somnolence. We found three reports, totalling five patients with acute exacerbations of TN, responding to intravenous infusion of phenytoin or fosphenytoin, with pain relief lasting two days [50-52], but no RCT has been conducted. We found no reports supporting the use of opioids in acute exacerbations of TN.

Clinical guide

In acute exacerbations, in-hospital treatment may be necessary for titration of anti-epileptic drugs and rehydration. Acute pain relief is crucial for affording a window of opportunity to adjust oral drugs and to control pain in consideration of a possible neurosurgical intervention. It is clinical experience that opioids are not effective in acute exacerbations of TN. It is clinical experience that intravenous infusion of fosphenytoin and lidocaine is effective for pain relief of acute exacerbations, but evidence is lacking. The intravenous infusion should be performed only under specialist supervision because hospital admission and cardiac monitoring are required.

Final recommendations

Given the very low quality of evidence there is weak recommendation for the use of intravenous fosphenytoin and lidocaine in acute exacerbations of pain.

Clinical question 2.2: For patients with primary TN, which drugs have demonstrated to be effective for the treatment of pain in the long term?

PICO:

Population: patients with primary TN

Intervention: most used drugs

Comparison: no treatment or most used drugs

Outcome: reduction of pain to an acceptable level with acceptable side effects for the patient (grade of importance: critical)

Search strategy

Criteria for inclusion were: published systematic reviews and RCTs, at least single-blinded and containing more than 10 individuals, of whom more than 80% were followed up. For GRADE evaluation please see Table 2.2. Results for each of the relevant drugs:

Carbamazepine

Results

From the systematic reviews [53] and RCTs [54-58], carbamazepine seems to be more effective at relieving pain compared with placebo but more patients withdrew when using carbamazepine than placebo because of side effects. All the RCTs were small and short-term although some converted to open label follow up, used simple measures for pain outcomes, and reported no quality-of-life outcomes. One RCT showed improved outcome if ropivacaine injections were added [59].

Clinical guide

Carbamazepine is considered the gold-standard for the initial medical treatment of TN. Carbamazepine has been shown to increase pain relief compared with placebo, but also causes adverse effects, such as drowsiness, dizziness, rash, liver damage and ataxia, and has the potential for multiple drug interactions. Consensus expert opinion suggests that carbamazepine may have a 50% failure rate for long-term (5-10 years) pain control [58, 60]. Based on the strength of published evidence, carbamazepine remains the best supported standard medical treatment for TN.

Recommendation

Based on a moderate quality of evidence, a strong recommendation is given that carbamazepine is used for long term treatment of TN.

Oxcarbazepine

Results

We found no fully reported RCTs on oxcarbazepine in TN. We found one small RCT comparing oxcarbazepine and carbamazepine at relieving pain after 4 to 6 weeks of treatment [61]. One non-systematic review [62] found that oxcarbazepine and carbamazepine were associated with similar reductions in attacks (pain, global symptoms) of TN, however oxcarbazepine may possibly be associated with fewer side effects than carbamazepine but both drugs show reduced tolerability in females [63].

Clinical guide

Oxcarbazepine is considered effective for the treatment of TN. We do not know how oxcarbazepine and carbamazepine compare at relieving pain. Clinical experience suggests both the effect and side effects may differ for the individual patient when treated with carbamazepine and oxcarbazepine [63]. Cross allergy between the drugs is reported.

Recommendation

Based on a very low quality of evidence, but high confidence from clinical experience of the effect of oxcarbazepine in TN, a strong recommendation is given that oxcarbazepine is used for long term treatment of TN.

Lamotrigine

Results

We found one small double-blind crossover RCT comparing the add-on of lamotrigine versus placebo in patients receiving carbamazepine or phenytoin [64]. Lamotrigine was possibly superior to placebo after 2 weeks of treatment [64].

Clinical guide

Lamotrigine may possibly be associated with fewer side effects than carbamazepine and oxcarbazepine. Lamotrigine can be used in patients who cannot tolerate carbamazepine and oxcarbazepine, or in addition to carbamazepine or oxcarbazepine when the latter become less effective. The dose of lamotrigine must be escalated slowly in order to avoid rashes, and it is therefore not appropriate for acute management of TN.

Recommendation

Based on a very low quality of evidence, a weak recommendation is given that lamotrigine is used either as monotherapy or as add-on therapy for long term treatment of TN.

Gabapentin

Results

We found one systematic review [65], which was based on 16 RCTs, all published in Chinese, comparing gabapentin with carbamazepine. However, the diagnostic criteria used are not clarified and the dosages used varied. Gabapentin is probably associated with fewer adverse effects than carbamazepine and oxcarbazepine.

Clinical guide

Clinical experience shows that gabapentin has lower effect but also fewer adverse events than carbamazepine and oxcarbazepine. Gabapentin can be used in patients who cannot tolerate carbamazepine and oxcarbazepine, or in addition to carbamazepine or oxcarbazepine when the latter become less effective.

Recommendation

Based on low quality of evidence, a weak recommendation is given that gabapentin is used either as monotherapy or as add on therapy for long term treatment of TN.

Botulinum toxin type A (Botox)

Results

We found one systematic review [66] which includes RCTs. The dosage used varied from 25U to 100U. There is some evidence that at 12 weeks botolinum toxin type A may result in a 50% decrease in pain severity and frequency with continuation of other systemic drugs. The source, dosage and method of administration are highly variable. An open label study found that 25% of patients remain pain free at 14 months post injection [67].

Clinical guide

There is limited clinical experience, but it is possible that botulinum toxin type A may have an effect as an add-on therapy in some selected cases.

Recommendation

Based on very low quality of evidence, a weak recommendation is given that botulinum toxin type A is used as add on therapy for medium term treatment of TN.

Other drugs

It is clinical experience that pregabalin, baclofen and phenytoin may have an effect in TN. The addition of ropivacaine injection to either carbamazepine or gabapentin may have an effect. We found no good evidence of benefit from any RCTs regarding these drugs.

Final recommendations on pharmacological treatment

In acute exacerbations, in-hospital treatment may be necessary for titration of anti-epileptic drugs, rehydration and intravenous infusion of fosphenytoin or lidocaine. For long-term treatment carbamazepine (200-1200 mg/day) or oxcarbazepine (300-1800 mg/day) remain the most effective medications especially in the early stages of TN. Sometimes even higher doses are needed. Retard (slow release) preparations are available but there are no studies to compare them with the conventional forms. However, if these drugs become ineffective or result in poor tolerability, then other drugs need to be considered. Based on low to very low quality of evidence, lamotrigine, gabapentin, botolinum toxin type A, pregabalin, baclofen and phenytoin may be used either as monotherapy or combined with carbamazepine or oxcarbazepine when first line drugs fail due to either efficacy or tolerability. Patients should be encouraged to alter the dosages depending on pain severity and side effects, as periods of partial or complete remission do occur [68]. However, it is crucial that patients are instructed to increase and decrease dosages slowly over several days. It is not essential to try out all the drugs prior to referral for a neurosurgical opinion. It remains the responsibility of the managing doctor to ensure the patient is aware of neurosurgical options and can take an informed decision about choice of treatment.

SECTION 3: SURGICAL TREATMENT

Clinical question 3.1: For patients with primary TN, how many drugs have to be tested before surgery should be offered?

Search strategy and results

We searched for studies with a minimum of 25 patients evaluating the optimal time for TN patients being offered surgery, and more specifically how many drugs need to be tried before the option of surgery should be offered. No studies were identified addressing this topic. We identified three descriptive studies dealing with the broader question as to when surgery should be offered [68-70].

The studies indicated that patients with TN refractory to medical therapy would possibly prefer an early surgical option. In a series of 156 TN patients, most patients (88%) preferred a surgical option to medical management [71]. One prospective study [72] reported that 65% of patients referred to a specialist centre could be satisfactorily managed medically 2 years after referral, whilst 35% were referred to surgery. A retrospective study of 200 patients managed medically for TN revealed that only a minority experienced a worsening of pain over time and/or development of late resistance [73].

Clinical guide

Based on expert opinion, medical management with adequate doses and regular monitoring is recommended before offering surgery for TN. Existing data indicate that not all patients need surgery, but also that some patients may be referred for surgery too late. No data indicate how many drugs must be tested before surgery should be offered.

Final recommendations

Based on a very low quality of evidence, medical management is recommended before offering surgery for TN. Patients should be offered surgery if their pain is not sufficiently controlled medically or if medical treatment is poorly tolerated and should be informed of the possibility at an early stage.

Clinical question 3.2: Which surgical technique gives the longest pain free period with the fewest complications?

Search strategy and results

We searched up to January 2018 for trials involving MVD, other posterior fossa surgery (partial sensory rhizotomy (PRS) and internal neurolysis (IN)), gamma knife surgery (GKS), radiofrequency thermocoagulation (RFTC), balloon compression (BC) and glycerol rhizolysis (GR). Two different search targets were defined: (i) comparative trials involving any two of the above interventional treatments, (ii) clinical trials of each surgical intervention separately. To be included in the analysis a comparative trial had to involve only patients with classical or idiopathic

TN with a minimum of 1-year follow-up and report the outcome as the proportion of patients free of pain (BNI score of I) or occasional pain but no need for medication (BNI II). For single intervention studies the following criteria for acceptable studies were set: a. minimum of 3-year follow up period; b. minimum of 25 patients treated for TN; c. study dealing with classic or idiopathic TN; d. diagnostic criteria stated; e. definition of success presented; f. definition of recurrence presented; g. duration of follow up period with range and mean presented; h. explicit definition of outcome measure used; i. mortality rate stated; and j. report of complications. For GRADE evaluation please see Tables 3.2a, 3.2b and 3.2c.

MVD vs. neuroablative treatments

No randomised controlled trials were identified. We found four non-randomised prospective studies, comparing the long-term (>1-year) impact of first-time MVD versus first-time GKS totalling 561 patients (MVD, N=287 and GKS, N=274) [74-77]. All studies showed superiority of MVD over GKS with a substantial effect size at both medium and long-term (see Table 3.2a). At 1-2 years postoperatively, 68-88% of patients who underwent MVD reported being free from pain with no need for medication (BNI I), while 24-71% did so after GKS. At 4-5 years, the percentages were 61-88% for MVD and 33-56% for GKS. Four non-randomised retrospective studies involving a total of 957 patients demonstrated a similar superiority of first-time MVD over GSK both at medium and long-term (Table 3.2b) [78-81]. Three systematic reviews comparing published results from independent treatment cohorts using various inclusion criteria demonstrated a longer postoperative pain free status for MVD compared to GKS [82-84]. One non-randomised prospective study evaluated the outcomes at 3 years after MVD versus GR or RFTC [85], showing MVD providing a greater percentage of pain-free status at 36 months compared to GR and RFTC. A retrospective study with 2-3 years' follow up showed that significantly more patients were completely pain-free after MVD than BC [86].

Comparison of neuroablative treatments

We were unable to find any randomised or non-randomised studies fulfilling the above inclusion criteria that compared long-term effectiveness between GKS, GR, BC and RFTC.

Single intervention trials

No randomised controlled trials were identified. We found 45 non-randomised cohort studies fulfilling the search criteria (7, 3, 5, 8, 1, and 21 studies for RFTC, GR, BC, GKS, IN and MVD, respectively) (Table 3.2c). Accepting some variability in the duration of observation periods across procedures, there appears a trend in favour of MVD with a median of 77% (range 62-89%) of patients being pain free at long-term follow up. The same percentages for IN, GKS, BC, RFTC and GR are 72, 58 (30-66), 68 (55-80), 58 (26-82) and 28 (18-59) respectively. None of the case series on effectiveness of PSR fulfilled inclusion criteria. For more details see supplementary material.

Complications

Reported complication rates from cohort studies are summarised in Table 3.2d. For more details see supplementary material. Only MVD is associated with reported mortality, although anecdotally it is known that RFTC and BC have in the past very rarely resulted in the patient's death. The distribution of complications reflects the nature of the operation. The small number of complications associated with GKS is noteworthy. Most of the reported complications are transitory and severe permanent adverse effects are rare. It should be also emphasised that facial hypaesthesia following neuroablative treatments tends to be associated with a better long-term response than any lack thereof. To help a comparison of the diverse complications across all interventions, an attempt has been made to assess their impact on the patient's health-related quality-of life [82]. The expected utility scores measuring this effect were reported as similar between MVD and GSK [82].

Clinical guide

Although the quality of published studies reviewed comparing MVD and GKS was low or very low, it is striking that they consistently showed superiority of MVD over GKS in classical and idiopathic TN, with comparable complication rates. In fully informed patients with classical TN with no previous operations, who have failed pharmacotherapy and who are willing to and can safely undergo neurosurgery, MVD is likely to provide a longer lasting postoperative pain-free state than GKS. Low quality evidence from two comparative studies and indirect data from cohort studies indicate that MVD may be considered more effective in providing relief from pain than RTFC, BC and GR. Due to limited and conflicting results, no preference can be shown for any one percutaneous neuroablative procedure over another. It should be underlined that they all do show considerable effectiveness and should be considered for those patients who cannot or prefer not to undergo MVD.

Final recommendations

Based on low quality evidence but extensive clinical experience, a strong recommendation is given that MVD is preferred over GKS in patients with classical TN who are willing to and can undergo posterior fossa surgery. Based on low quality evidence, a weak recommendation is given that MVD may be considered preferential over other neuroablative treatments (RTFC, BC, IN and GR). No recommendation can be given for choice between any neuroablative treatments, or between them and MVD when an MRI scan fails to show significant nerve compression (idiopathic TN). Neuroablative treatments should be the preferred choice, if MRI does not demonstrate any NVC.

SECTION 4: MANAGEMENT OF SECONDARY TN AND NON-PHARMACOLOGICAL AND NON-SURGICAL MANAGEMENT OF TN.

Clinical question 4.1: Should patients with secondary TN be offered the same pharmacological and surgical treatments of pain as patients with primary TN?

Search strategy and results

We searched for reports containing the key words "secondary trigeminal neuralgia" or "symptomatic trigeminal neuralgia", AND treatment or management. One systematic review [87] but no RCTs were found for the medical treatment of secondary TN, but a few small case series reported successful treatment with lamotrigine [88-90], carbamazepine [89], misoprostol [91, 92], gabapentin [93], topiramate [94, 95] and botulinum toxin type A [96]. Most of these studies investigated TN secondary to MS. Surgical treatment was evaluated in secondary TN with only a small case series reporting treatment outcomes, with a general tendency toward lesser efficacy in this population. Most authors recommend the use of Gasserian ganglion procedures unless a definitive vascular compression of the trigeminal nerve is identified on MRI. Radiofrequency thermocoagulation can be considered in secondary TN following dental procedures [97]. Case reports conveyed a benefit of MVD for patients with MS but suggest less efficacy than in non-MS patients [98, 99]. A retrospective cohort study investigating 15 patients with MS over a median observation period of 55 months (range 17-99 months) reported that 7 (47%) were completely paroxysm-free and that an additional 4 (27%) had significant relief (>50%) of episodic pain.

Among the eight patients with a constant pain component, all were free of their constant pain and 4 (50%) were free of their episodic pain [100]. Electrical transcutaneous stimulation was reported to be effective in patients with primary and secondary TN, but the authors did not clearly distinguish between patient types when evaluating outcomes [101].

Clinical guide

Patients with secondary TN generally respond less well to conventional or surgical treatment. As no treatment has sufficient evidence to prove its specific efficacy in secondary TN patients, they should be treated similarly to patients with primary TN. Gasserian ganglion procedures can be considered. In patients with MS, when a definite NVC is present on MRI, an MVD could be considered.

Final recommendation

Based on a very low quality of evidence, medical treatment of patients with secondary TN should be similar to those with primary TN. Surgical interventions should consider Gasserian ganglion procedures and MVD.

Clinical question 4.2: For patients with primary TN, what other non-pharmacological and non-surgical support can be provided?

Search strategy and results

We searched for papers evaluating the overall disability caused by TN and how this can be managed by means other than drugs and surgery. There is increasing evidence that depression, anxiety and poor coping mechanisms are common in patients with TN and result in poor quality of life [68, 102-105]. These features are further compounded by the effects of the medications and complications after surgical treatments. There is good evidence that cognitive behavioural therapy is effective for chronic pain [106] and that self-management interventions for migraine and tension-type headache can be better than the usual care provided [107]. An evaluation of three patient-organised national meetings in the UK, USA and Australia showed that these are highly valued by sufferers as an opportunity to improve their knowledge and understanding [108].

Clinical guide

It is important to take into consideration that patients with TN suffer not only from severe pain but also from other factors such as depression and anxiety. A small pilot study using a group cognitive behaviour program has been run in the UK and has been highly evaluated. This has now been supplemented by a telephone service offered by a clinical nurse specialist who can also prescribe, and patients have found this very helpful. These programs enable patients to meet fellow sufferers and develop strategies for coping with flare-ups, which may result in fewer visits to emergency services and primary care doctors. Support groups run by TN sufferers were first established in the US and UK and now also run in Australia, Canada, Denmark, Germany, Spain and France. Sufferers report a great need for the support and advice that they can obtain from support group volunteers who understand the needs of this community. Regular contact with members and others through telephone and email helplines, web-based forums, local groups, national meetings and conferences can be very helpful for those patients.

Final recommendations

Based on very low quality of evidence, it is recommended that patients are offered psychological and nursing support. Patients should be directed to national support groups where these are present.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The diagnostic criteria for TN have changed considerably, since publication of the previous AAN-EFNS guideline, in order to avoid the differences between the criteria laid out by IHS and IASP. The recent ICHD diagnoses TN as primary TN, either classical or idiopathic depending on the degree of neurovascular contact, or as secondary TN caused by other than neurovascular contact. We recommend that MRI is used as part of work up in TN patients, because no clinical characteristics can exclude secondary TN. We recommend using a combination of three high-resolution sequences - 3D T2-weighted, 3D TOF-MRA and 3D T1-Gad. The neuroradiologist should be blinded to the side of pain and should describe whether a vessel contact causes morphological changes of the nerve. If MRI is contraindicated or unavailable, trigeminal reflexes can be used to distinguish secondary TN from primary TN. Neurovascular contact plays an important role in primary TN, but demonstration of a neurovascular contact should not be used to

confirm the diagnosis of TN. Rather, it may help to decide if and when a patient should be referred for MVD.

In acute exacerbations of pain, in-hospital treatment may be necessary for titration of anti-epileptic drugs, rehydration and intravenous infusion of fosphenytoin or lidocaine. For long-term treatment we recommend carbamazepine or oxcarbazepine as drugs of first choice. Lamotrigine, gabapentin, botolinum toxin type A, pregabalin, baclofen and phenytoin may be used either as monotherapy or combined with carbamazepine or oxcarbazepine. Patients should be encouraged to adjust the dosages depending on pain severity and side effects and should be given specific instructions on titration. We recommend that patients should be offered surgery if pain is not sufficiently controlled medically or if medical treatment is poorly tolerated. MVD is recommended as first line surgery in patients where NVC with morphological changes has been demonstrated (classical TN). No recommendation can be given for choice between any neuroablative treatments or between them and MVD when an MRI scan fails to show NVC with morphological changes (idiopathic TN). Neuroablative treatments may be preferred if MRI does not demonstrate any NVC. Treatment for patients with secondary TN should in general follow the same principles as for primary TN. In addition to medical and surgical management, we recommend that patients are offered psychological and nursing support.

Compared with the previous AAN-EFNS guideline, there are important changes regarding diagnosis and imaging. This allows better characterization of patients and helps in decision making regarding the planning of medical and surgical management. Recommendations on pharmacological and surgical management have been updated. Unfortunately, no substantial progress in management has been made since the previous guideline.

There is a great need for future research in the pathophysiology and prognosis of TN and for development of more standardized outcomes, including quality of life, to allow for a more reliable comparison of results from different studies. Pharmacological management should be evaluated using modern standards and there is a huge need for development of more effective drugs with fewer side effects than current medications. We need prospective studies evaluating outcome after surgery using independent assessors as well as studies comparing the various surgical procedures, and studies comparing these to pharmacological management. Management of secondary TN should be explored, and non-pharmacological and non-surgical treatment options should be evaluated.

Fortunately, there is increased interest and research in TN. This will hopefully result in improvements, making an update of this guideline necessary in the not too distant future. It is likely that this guideline will need to be updated in 2025.

SUPPLEMENTARY MATERIAL

Appendix S1: Clinical question 1.3.

Appendix S2: Clinical question 3.2.

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Table 1.1. Diagnostic accuracy of clinical features for distinguishing secondary trigeminal neuralgia (STN) from primary (classical and idiopathic) trigeminal neuralgia (PTN).

First author	Year	Design	Spectrum	PTN STN	Number	Age of onset ±SD	Current age ±SD	Sensory deficits	First division	Bilateral	Poor rx response
Liu	2017	CO P	Narrow	PTN	2035	61*	63±13	-	-	10/2035	-
				STN	35 (masses)	48*	52±13	-	-	0/35	-
Truini	2016	CO P	Broad	PTN	149	60±12	-	0/149	-	- **	-
				STN	28 (MS)	50±8	-	14/28	-	-	-
Cruccu	2006	CO P	Broad	PTN	96	62±12	-	0/96	28/96	0/96	-
				STN	24 (mixed)	51±10	-	2/24	9/24	0/24	-
De Simone	2005	CC P	Narrow	PTN	13	60±12		4/13	8/13	0/13	-
				STN	15 (MS)	43±11		10/15	3/15	0/15	-
Sato	2004	CO R	Broad	PTN	43	-	-	-	-	-	3/43
				STN	7 (masses)	-	-	-	-	-	2/7
Goh	2001	CO R	Broad	PTN	36	-	60±13	0/36	-	0/36	-

Author	Year	Study	Definition	TN type	N	Age					
				STN	6 (masses)	-	53±11	1/6	0/6	0/6	1/6
Hooge	1995	CS R	Narrow	PTN	0	-		-	-	-	-
				STN	35 (MS)	51		3/23	-	5/35	2/22
Nomura	1994	CO R	Broad	PTN	58	47±13		1/26	11/58	-	-
				STN	22 (masses)	48±16		6/16	6/22	-	-
Pooled				P assos	< 0.0001	< 0.0001		< 0.0001	0.971	< 0.0001	0.631
				Sen (CI)				32 (24-42)	27 (17-39)	4 (1-10)	14 (5-30)
				Spe (CI)				98 (96-99)	72 (64-79)	100 (99-100)	93 (81-99)
				Pos LR				20.6	1.0	9.5	2.1

PTN: Primary (idiopathic and classical) trigeminal neuralgia, STN: secondary trigeminal neuralgia, MS: multiple sclerosis, CO: cohort survey, CC: case control, CS: case series, P: prospective data collection, R: retrospective or not described data collection, CI: 95% confidence interval, P assoc: probability of statistically significant association between the presence of the characteristic and the presence of STN, Sen: sensitivity. Sensitivities calculated for the presence of the characteristic in STN, Spe: specificity. Specificities calculated for the absence of the characteristic in CTN. Pos LR: positive likelihood ratio, NS: not significant. * Approximated estimates based on symptom duration extracted from current age. SD not available. ** Bilateral trigeminal neuralgia excluded a priori.

Table 1.2a. Diagnostic accuracy of trigeminal reflex testing for distinguishing secondary TN (STN) from primary TN (PTN).

First author	Year	STN A/T	PTN A/T	P assoc	Spe (CI)	Sen (CI)
Kimura	1970	1/1	1/14	NS	93%	100%
Ongerboer de Visser	1974	16/16	0/11	< 0.0001	100%	100%
Kimura	1983	10/17	4/93	< 0.0001	96%	59%
Cruccu	1990	4/4	2/30	< 0.0003	93%	100%
Cruccu	2006	23/24	7/96	< 0.0001	93%	96%
Cruccu	2009	41/46	-	NS	-	89%
Squintani	2015	-	0/11	NS	100%	-
Liao	2010	-	3/49	NS	94%	-
Pooled		95/108	17/304	< 0.0001	94% (91 to 96)	88% (80 to 93)

Table 1.2b. Diagnostic accuracy of evoked potentials for distinguishing secondary TN (STN) from primary TN (PTN).

First author	Year	Method	STN A/T	PTN A/T	P assoc	Spe (CI)	Sen (CI)
Leandri	1988	electrical-TEPs	18/23	9/38	<0.0001	76%	78%
Cruccu	1990	electrical-TEPs	4/4	9/30	< 0.05	70%	100%
Cruccu	2001	laser-EPs	20/20	24/47	<0.0001	49%	100%
Mursch	2002	electrical-TEPs	6/10	13/37	NS	65%	60%
Squintani	2015	laser-EPs		11/11	NS	0	
Obermann	2007	PREPs		24/24	NS	0	
Pooled			48/57	90/187	<0.0001	52% (45 to 59)	84% (73 to 91)

Table 1.3a. Prevalence, associations, sensitivity and specificity of MRI-verified neurovascular contact of any type and with morphological changes in patients with primary (idiopathic and classical) trigeminal neuralgia.

Author	Year	MRI field strength	Nº	Symp NVC	Asymp NVC	Odds ratio	P value	Sen (Cl) %	Spe (Cl) %	Symp NVC+MC	Asymp NVC+MC	Odds ratio	P value	Sen (Cl) %	Spe (Cl) %
Masur*	1995	1.5 T	16	10	6	5.0	0.221	63	62	7	0	15.0	0.023	44	100
Maarbjerg**	2014	3.0 T	135	120	105	2.0	0.014	89	22	71	18	11.6	<0.001	53	87
Antonini**	2014	1.5 T	24	21	9	7.0	0.006	88	63	16	2	15.0	0.001	67	92
Pooled Confidence interval			175	151	120	3.2 (1.7-6.3)	<0.001	86 (80-91)	31 (25-39)	94	20	13.3 (5.8-30.6)	<0.001	54 (46-61)	89 (83-93)

Nº: number of patients. T: Tesla. Symp NVC: number of neurovascular contacts of any kind on the symptomatic (painful) side. Asymp NVC: number of neurovascular contacts of any kind on the asymptomatic (pain-free) side. NCV+MC: neurovascular contact with morphological changes. Morphological changes were defined as compression, distortion, dislocation or atrophy of the trigeminal nerve at the site of a neurovascular contact. * The study is based on 18 patients but in 2 patients NVC status was not judge able due to artefacts. To enable calculation of odds ratio for NVC+MC 0.5 was added to each cell. ** For the purpose of this guideline the authors provided the original datasets.

Table 1.3b. Association between neurovascular contact without morphological changes and the symptomatic side in idiopathic trigeminal neuralgia and association between neurovascular contact with morphological changes and the symptomatic side in classical trigeminal neuralgia.

Author	Idiopathic trigeminal neuralgia					Classical trigeminal neuralgia				
	Nº	Symp NVC	Asymp NVC	Odds ratio	P value	Nº	Symp NVC+MC	Asymp NVC+MC	Odds ratio	P value
Masur*	9	3	2	2.0	1.000	7	7	0	15.0	0.034
Maarbjerg**	64	49	47	2.4	0.021	71	71	18	11.6	<0.001
Antonini**	8	5	3	2.0	0.344	16	16	2	15.0	0.001
Pooled	81	57	52	2.3	0.008	94	94	20	13.3	<0.001
Confidence interval				(1.2-4.3)					(5.8-30.6)	

Nº: number of patients. Symp NVC: number of neurovascular contacts of any kind on the symptomatic (painful) side. Asymp NVC: number of neurovascular contacts of any kind on the asymptomatic (pain free) side. NCV+MC: neurovascular contact with morphological changes. Morphological changes were defined as compression, distortion, dislocation or atrophy of the trigeminal nerve due to a neurovascular contact. * The study is based on 18 patients but in 2 patients NVC status was not judge able due to artefacts. For the calculation of odds ratio for NVC+MC 0.5 was added to each cell. ** For the purpose of this guideline the authors provided the original data sets.

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Table 2.2. GRADE evaluation of pharmacological treatment studies in primary TN.

Studies (participants)	Outcome	Comparison	Design	Quality	Effect size	GRADE quality of evidence	Direction	Strength	Comment
Wiffen (208)	Pain relief	Carbamazepine up to 2400 mg versus placebo	RCT	-3	+2	Moderate	For	Strong	Quality points deducted for crossover design and short follow-up; directness point deducted for inclusion of different pain severities and uncertainties about diagnostic criteria and outcomes measured; effect-size points added for RR=5 or higher
Liebel (48)	Pain relief	Oxcarbazepine 750 mg versus carbamazepine	RCT	-3	0	Very low	For	Strong	Quality points deducted for sparse data, incomplete reporting of results, and no direct comparison between groups
Zakrzewska (14)	Pain relief	Lamotrigine 400 mg as add on versus placebo	RCT	-3	0	Very low	For	Weak	Quality points deducted for sparse data and crossover design with no pre-crossover results; directness point deducted for concurrent use of other medications
Yuan (1,331)	Pain relief	Gabapentin up to 3600 mg versus	RCT	-3	+1	Low	For	Weak	High risk of bias, wide confidence limits

		carbamazepine							
Morra (178)	Pain relief	Botox versus placebo, variable doses	R C T	-3	0	Very low	For	Weak	Variable techniques, dosages, varying time periods, quality points deducted for risk of bias, small sample sizes, similar age and duration of symptoms but other drug usage unknown, missing data

Table 3.2a. Prospective trials comparing microvascular decompression (MVD) and gamma knife surgery (GKS).

Author	MVD (N) GKS (N)	Outcome* 1-year	Outcome* 1.5-years	Outcome* 2-years	Outcome* 4-years	Outcome* 5-years	K-M curve Log rank,	RR	GRADE
Brisman 2008	MVD (24) GKS (61)	MVD 68% GKS 58%	MVD 68% GKS 24%				p=0.089		low
Linskey 2008	MVD (36) GKS (44)			MVD 88% GKS 50%		MVD 80% GKS 33%	p=0.0002	3.35	low
Pollock 2010	MVD (91)** GKS (49)	MVD 84% GKS 66%			MVD 77% GKS 56%		p=0.003	2.25 (1.4-4.6)	low
Wang 2017	MVD (136) GKS (120)	MVD 83% GKS 71%				MVD 61% GKS 47%	p=0.006		low
				Outcome 1-2 years		Outcome 4-5 years			
Total	MVD (287) GKS (274)	MVD 68-84%		MVD 68-88%		MVD 61-80%			low

		GKS 58-71%		GKS 50-71%		GKS 33-56%			

*Outcome, percentage of patients pain-free on no medication.   **PFE; 91% has MVD

Table 3.2b. Retrospective trials comparing microvascular decompression (MVD) and gamma knife surgery (GKS).

Author	MVD (N) GKS (N)	Outcome time point	Outcome	GRADE
Oh 2008	MVD (27) GKS (18)	33 mo (mean)	MVD 63% GKS 56%	Very low
Dai 2016	MVD (87) GKS (115)	2 years	MVD 72% GKS. 60%	Very low
Nanda 2015	MVD (20) GKS (49)	5.3 years (median)	MVD 75% GKS. 37%	Very low
Inoue 2017	MVD (179) GKS (52)	3.3 years (median) 5.0 years (median)	MVD 80% GKS 39%	Very low

Table 3.2c. Summary of outcomes from single intervention trials.

Intervention	No. studies	Total no. patients	Mean/median F/U, years	Pain free at F/U, %	GRADE
MVD	21	5149	3 – 10.9	62 - 89	Very low
GKS	8	1168	3.1 – 5.6	30 - 66	Very low
RFTC	7	4533	3 – 9.3	26 – 82	Very low
BC	5	755	4.2 – 10.7	55 - 80	Very low
GR	3	289	4.5 - 8	19 - 58	Very low
IN	1	26	3.6	72	Very low

MVD: microvascular decompression. GSK: gamma knife surgery. RFTC: radiofrequency thermocoagulation. BC: balloon compression. GR: glycerol rhizolysis. IN: internal neurolysis.

Table 3.2d. Reported complications from included cohort studies.

Intervention	N	Mortality	Cerebral	Hearing loss	Facial hypaesth	Corneal hypaesth	V motor weakness	AD	Kerat-itis	CN palsy	CSF leak	Mening itis	HS
MVD	5149	15	32	95	147	17		1		211	101	20	16
GKS	1168	0			184				3	2			
RFTC	4533	0		6	853	300	280	29	55	36	5	1	
BC	755	0			110	5	34	1	1	12		43	
GR	289	0		1	115	19	5	2					
IN	26	0	0	0	25	0	0	1	0	0	1	0	0

MVD: microvascular decompression. GSK: gamma knife surgery. RFTC: radiofrequency thermocoagulation. BC: balloon compression. GR: glycerol rhizolysis. IN: internal neurolysis. Cerebral: oedema, haemorrhage, stroke. Hypaesth: hypaesthesia. AD: anaesthesia dolorosa. HS: herpes simplex.

Supplementary material for Clinical question 1.3: What role does neurovascular contact play in primary trigeminal neuralgia?

Search strategy

We searched for full reports written in English of prospective studies of broad spectrum CTN and ITN patients published in peer-reviewed journals since 2006 comparing the masked symptomatic and asymptomatic side by high resolution MRI and grading the NVC as to whether there are morphological changes of the nerve or not.

After the publication of the included studies, the IHS and IASP published new classifications dividing what was previously termed CTN into CTN and ITN based on whether or not there is a NVC with morphological changes of the trigeminal root (1,2). Implicitly, this subclassification is decisive of how big a role an NVC play in ITN and CTN, respectively. As the original data from the included studies was available for the purpose of this guideline, the following clinical guide discusses both the importance of NVC in general and in CTN and ITN patients, respectively.

We defined "broad spectrum" to be CTN and ITN patients from neurological settings as, in general, only medically refractory patients with an NVC are referred to neurosurgery and thus included in neurosurgical papers. If the majority of patients were neurological patients, the paper was accepted, if this was not specifically accounted for, the study was excluded. We identified 3 studies fulfilling the search criteria (3–5). All three studies were prospective cohort studies.

GRADE

Level of evidence: **high quality of evidence**

Starting level was low as only observational cross-sectional studies goes into the analysis. Factors that raised the level for the quality of evidence were: a very large effect, a dose-response relationship (the higher degree of NVC, the stronger association). Total points to raise grade = 3. Risk of bias, indirectness, imprecision (although two studies included relatively few patients) and publication bias were not considered big problems. Inconsistency is an issue as the studies in some aspects yield differing estimates. This is probably explained by the different magnetic field strengths. Total points to reduce grade = 1.

Direction of the recommendation: **for**

It is associated with the greatest benefit and the lowest harm to know the status of NVC. It carries implications for treatment strategies and preoperative patient information.

Strength of recommendation: **strong**

Based on high quality of evidence, high degree of confidence that the desirable effects outweigh the undesirable effects, high certainty in no variation in values and preferences among patients or clinicians, recommendation not associated to higher costs and that advantages and disadvantages are clear. Adhering to the recommendation will do more good than harm.

Results

NVC of any kind was a frequent finding (151/175 asymptomatic nerves) (Table 1) on the asymptomatic side in TN patients while NVC with morphological changes was a rare finding on the asymptomatic side (20/175 asymptomatic nerves). ITN was weakly but significantly associated to a NVC without morphological changes on the symptomatic side (OR 2.3, p = 0.008) (Table 2). CTN was highly associated to NVC with morphological changes on the symptomatic side (OR 13.3, p < 0.001).

Clinical guide

TN is associated to NVC of any kind on the symptomatic side and highly associated to NVC with morphological changes on the symptomatic side. TN remain a diagnosis based on the clinical symptoms and signs and exclusion of a symptomatic cause (multiple sclerosis or a space-occupying lesion) by means of MRI, physical and neurological examination and patient history. As NVC, especially NVC without morphological changes, is a frequent variation of normal neuroanatomy, NVC is not to be used as a diagnostic tool to diagnose or exclude TN in facial pain patients.

As pooled analyses showed a weak but significant odds ratio in favor of an association between an NVC without morphological changes and the symptomatic side in ITN, it appears that NVC does play a role in the etiology of ITN patients, at least in a subset of patients who are therefore not truly "idiopathic". Notably, in ITN, and probably also to lesser degree in CTN, other currently unknown etiological factors contribute to or are responsible for the development TN.

It is plausible that CTN patients have a higher chance of a successful outcome after microvascular decompression, but high quality prospective neurosurgical studies using independent assessors of outcome are missing to support this hypothesis.

Final recommendations

Based on a high quality of evidence, a strong recommendation is given that ITN is weakly associated to NVC without morphological changes and that CTN is highly associated to NVC with morphological changes. Demonstration of NVC should not be used to confirm or refute the diagnosis of TN. Rather; it may help guide treatment decisions.

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Supplementary material for Clinical question 3.2: Which surgical technique gives the longest pain free period with fewest complications?

Search Strategy

All of the literature on the surgical management of trigeminal neuralgia (TN) was searched with electronic databases from January 1990 until January 2018, using Medline, Embase, and the Cochrane Library, including the references of the reported studies. The diagnostic terms used were as follows: trigeminal neuralgia, tic douloureux, facial neuralgia, surgical treatment, complications and long-term outcome. They were combined with the following surgical terms: radiofrequency thermocoagulation, partial sensory rhizotomy, internal neurolysis, eletrocoagulation, glycerol rhizotomy, balloon compression, stereotactic surgery, radiosurgery, and microvascular decompression.

The inclusion criteria were: 1. minimum of 3-year follow-up period; 2. minimum of 25 patients treated for classical TN; 3. study dealing with classic TN; 4. diagnostic criteria stated; 5. definition of sucess presented; 6. definition of recurrence presented; 7. duration of follow-up period with range and mean presented; 8. explicit definition of outcome measure used; 9. mortality rate stated; and 10. report of complications.

The evaluating measures of this study were the number of patients, number of interventions, sex, side of pain, distribution of pain, duration of symptoms (DOS) before surgery, average of follow-up (FU) period (mean), acute pain relief (APR) rate, follow-up pain free rate (PFR), recurrence or failure rates, and complications. Neuralgia was considered cured – and thus the surgical treatment a sucess – when relief was complete and all medication withdrawn. Neuralgia was considered partially relieved when some pain remained but well controlled by complementary drug therapy. The surgical treatment was considered a failure when pain persisted in any form, either spasmodic or constant aching pain, despite associated medical therapy.

Results

Of 1428 articles on surgical treatment of TN published after January 1990, only 45 non-randomised cohort studies met the inclusion criteria and were eligible studies, including 11920 patients [1, 3-7, 9, 11, 13-19, 22, 24-28, 31-33, 35-40, 42, 43, 45, 46, 48-54, 56-58]**.** No randomised controlled trials were identified. Evidence from direct comparisons between different surgical procedures is insufficient (see references in

clinical question 3.2). Demographics of the patients and pain relief data included in our analysis can be found in Tables 1-6 and complications in Tables 7-12.

The following surgical procedures used in the treatment of TN were evaluated: a) Peripheral Techniques (Neurectomy, Cryotherapy, and Alcohol Injection); b) Percutaneous Procedures on the Gasserian Ganglion (Radiofrequency Thermocoagulation - RFT, Glycerol Rhizotomy - GR, and Percutaneous Balloon Compression - PBC); c) Gamma Knife Surgery - GKS; d) Internal Neurolysis (IN); and e) Microvascular Decompression - MVD.

a) Peripheral Techniques

Most of these procedures can be carried out under local anestesia and do not require the patients to be medically fit. All of these procedures depend on accurate assessment of which nerve branch is acting as the trigger área; surgery is then carried out on that branch [34]. There are no long-term longitudinal studies for these peripheral procedures. All studies are retrospective case series report [2, 10, 30, 44, 55]. It is difficult to compare results for peripheral surgeries from the current literature, especially in terms of pain relief, as variable techniques of analysis were used and end points were not clearly defined [34].

b) Percutaneous Procedures on the Gasserian Ganglion

Surgery at the Gasserain Ganglion level is achieved by a specially designed device inserted into the cheek. Under radiographic control, the device is directed through the foramen ovale into the Gasserian Ganglion or retrogasserain rootles and then controlled lesion of the trigeminal ganglion or root by various means: termal lesion (RFT) [47], chemical lesion with glycerol (GR) [12] or mechanical lesion with a balloon inflated into the Meckel's Cave (PBC) [29].

b.1) Radiofrequency Thermocoagulation

This percutaneous technique consists in achieving thermoalgic anesthesia of the painful territory by applying heat on the trigeminal nerve sensory axons. The currently accepted mechanism of action considers that the Aδ and C thermoalgic fibers (respectively weakly myelinated or amyelin fibers) are thermo-sensitive [47]. The seven eligible studies [5, 15, 16, 35, 48, 49, 54] included 4533 patients (Table 1). Three studies comprised 3737 (82%) patients [5, 16, 49]. The average FU varied from 3 to 9.3

years. The APR rate was achieved in more than 90%. The reported FU pain free and recurrence or failure rates of RFT ranged from 26-82% and 16-74%, respectively. The reported most important complications of this group were facial hypoesthesia or paresthesia, corneal hypoesthesia, keratitis, trigeminal motor weaknesscranial, anaesthesia dolorosa and cranial nerve palsy (Table 7).

b.2) Glycerol Rhizotomy

This technique is based on the neurotoxic effect of glycerol coming contact with the post-gasserian fibers of the trigeminal nerve [12]. In this surgical modality, there were only three studies (Table 2) indicating the outcome of 289 patients in total with a FU ranging from 4.5 to 8 years [11, 35, 45]. The APR rate was achieved in aproximatively 75%. The reported PFR at mean FU decreased to 18-59% (mean: 40%) and recurrence or failure rates varied from 41 to 84%. The most important complication of these GR studies was facial hypoesthesia or paresthesia (Table 8).

b.3) Percutaneous Balloon Compression

The principle of this technique is that compression of the retrogasserian fibers of the trigeminal ganglion in Meckel's caves injures in priority small amyelin and weakly myelinated nociceptive fibers [29]. The literature search yielded 5 studies [6, 7, 24, 33, 43] that met the inclusion criteria for this treatment (Table 3). The average FU varied from 5 to 10.7 years. The APR rate was achieved in more than 95%. The reported PFR at mean FU decreased to 54.5-80% (mean: 67%) and recurrence or failure rate varied from 20% to 51.7%. The reported most important complications of this group were facial hypoesthesia or paresthesia in 14.6% (110/755 patients) and trigeminal motor weakness in 4.5% (34/755 patients) (Table 9).

c) Gamma Knife Surgery

Invented by Lars Leksel [23], this is the only non-invasive technique, which aims a focused beam of radiation at the trigeminal root in the posterior fossa. A stereotaxic apparatus is positioned under local anesthesia followed by CT and MRI to obtain a 3D localization of the target zone. We found 8 studies (Table 4) which used independent outcome assessment and provided long-term FU [9, 13, 14, 25, 26, 37, 38, 52]. These studies comprised 1168 patients. Various patient series reported comprised of less than 25 patients or FU of less than 3 years and were eliminated. In the selected series, the

radiation dose varied from 75 to 95 Gy. Six of 8 studies reported more than 20% of patients that had prior surgical procedures before GKS [9, 13, 25, 26, 37, 38]. The average FU varied from 3.2 to 5.6 years. The APR rate was achieved in less than 80%. The reported PFR at mean FU decreased to 36-91.7 % (mean: 60%) and recurrence or failure rates varied from 18% to 52.2%. The time to pain relief varied from 1 day to 24 months in these selected series. A wait for pain relief for "months" is clinically impractical because TN patients need speedier pain relief. The low incidence of morbidity was the greatest advantage of GKS compared with all other sugeries. In these studies, the major complication was facial hypoesthesia or paresthesia (184/1168 patients; 15.8%) (Table 10).

d) Internal Neurolysis

IN is a procedure in which all or portions of the trigeminal nerve are divided longitudinally along its fibers between the pons and the porus trigeminus. There is another option for treating TN in which no neurovascular compression is observed on imaging or during surgery. The literature search yielded only 1 study [18] that met the inclusion criteria for this treatment (Table 5). The average FU was 3.6 years. The APR rate was achieved in 85%. The reported PFR at mean FU decreased to 72% and recurrence rate was 27%. The reported most important complications of this group were facial hypoesthesia (96%), cerebral-spinal fluid (CSF) leak (4%) and anesthesia dolorosa (4%) (Table 11).

e) Microvascular Decompression

This a major neurosurgical procedure that entails craniotomy to reach the TGN in the posterior fossa. Vessels compressing the nerve are identified and moved out of contact. Some authors have instead emphasized the importance of physical impact of the blood vessel on the nerve [40, 42]. Long-term outcome after surgical revision of mere neurovascular contact is uncertain compared to the decompression of dislocated, distorted, or flattened nerve roots [1, 40, 41]. Advanced MRI techniques further allow for visualization of structural changes within the root that are highly suggestive of physical alteration and provide high predictive value for pain relief after decompression [20]. Diffusion tensor imaging (DTI) and fiber tractography detects abnormalities of the trigeminal nerve root that normalize following decompression or radiosurgery and may become an essential diagnostic test for TN before surgery [8, 21]. In this surgical

modality, there were 21 studies (Table 6) indicating the outcomes of 5149 patients in total [1, 3, 4, 17, 19, 22, 27, 28, 31, 32, 36, 39, 40, 42, 46, 50, 51, 53, 56-58]. The average FU varied from 3 to 10.9 years. The reported initial pain relief, FU pain free and recurrence rates of the MVD group range from 80-98.2%, 62-89% and 4-38%, respectively. However, the average initial pain relief, FU pain free and recurrence rates were calculated as 93.7%, 84% and 21.2%, respectively. The reported most important complications of this group were hearing loss, facial hypoesthesia or paresthesia, cranial nerve palsy and CSF leak (Table 12). The mortality rate was 0.3% (15/5149 patients).

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Table 1. Demographic of patients and pain relief data of RFT series

References	NP	Age (y)	Male (%)	Female (%)	R (%)	L (%)	Bil. (%)	DOS (y)	Average FU (y)	APR rate (%)	Follow-up PFR (%)	Recurrence or failure rate (%)
Broggi et al., 1990	1000	68	42	58	59	40.3	0.7	#	9.3	95	82	18
Taha and Tew, 1996	500	#	#	#	#	#	#	#	9	98	80	20
Oturai et al., 1996	185	71	#	#	#	#	#	#	8	83	49	49
Yoon et al., 1999	81	65	49	51	62	38	0	9	6	87	26	74
Kanpolat et al., 2001	1600	57	47.9	52.1	63	33	4	#	5	97.6	57.7	42.3
Huang et al., 2010	30	64	37	63	70	30	0	#	3	76.7	73.3	26.7
Tang et al., 2015	1137	61.5	40.6	69.4	57.1	40.8	2.1	7.2	3.8	98	72	16

RFT (Radiofrequency Thermocoagulation), NP (number of patients), R (right), L (left), Bil (bilateral), DOS (duration of symptons), y (years), APR (acute pain relief), PFR (pain-free rate), # (not clear)

Table 2. Demographic of patients and pain relief data of GR series

References	NP	Age (y)	Male (%)	Female (%)	R (%)	L (%)	Bil. (%)	DOS (y)	Average FU (y)	APR rate (%)	Follow-up PFR (%)	Recurrence or failure rate (%)
Fujimaki et al., 1990	122	71.7	41	59	#	#	#	#	4.5	78	28	72
Steiger, 1991	122	67	34	66	58	42	0	#	5	84	59	41
Oturai et al., 1996	45	54	#	#	#	#	#	#	8	42	18	84

GR (Glycerol Rhizotomy), NP (number of patients), R (right), L (left), Bil (bilateral), DOS (duration of symptons), y (years), APR (acute pain relief), PFR (pain-free rate), # (not clear)

Table 3. Demographic of patients and pain relief data of PBC series

References	NP	Age (y)	Male (%)	Female (%)	R (%)	L (%)	Bil. (%)	DOS (y)	Average FU (y)	APR rate (%)	Follow-up PFR (%)	Recurrence or failure rate (%)
Lichtor and Mullan, 1990	61	#	#	#	#	#	#	#	5	97	80	20
Skirving and Dan, 2001	496	#	56	44	#	#	#	#	10.7	100	68.1	31.9
Omeis et al., 2008	29	62.9	48	52	48	52	#	#	5.4	82.7	54.5	51.7
Campos and Linhares, 2011	39	62.3	46	54	84	16	0	7.5	4.2	93.5	80	20
Chen et al., 2011	130	61.3	48.5	51.5	61.5	38.5	0	10	8.9	93.8	62.3	37.7

PBC (Percutaneous Balloon Compression), NP (number of patients), R (right), L (left), Bil (bilateral), DOS (duration of symptons), y (years), APR (acute pain relief), PFR (pain-free rate), # (not clear)

Table 4. Demographic of patients and pain relief data of GKS series

References	NP	Age (y)	Male (%)	Female (%)	R (%)	L (%)	Bil. (%)	DOS (y)	Average FU (y)	APR rate (%)	Follow-up PFR (%)	Recurrence or failure rate (%)
McNatt et al., 2005	49	68	41	59	#	#	#	8.3	3.7	36	30	46
Urgosik et al., 2005	107	75	43	57	#	#	#	#	5	80.4	58	25
Longhi et al., 2007	160	63.4	45	55	#	#	#	8	3.1	61	#	18
Dhople et al., 2009	112	64	35	65	56	42	1	4.8	5.6	69	34	56
Han et al., 2009	60	61	37.5	72.5	#	#	#	7.7	4.8	90.2	63	52.2
Riesenburger et al., 2010	53	65.8	49	51	51	49	0	8	4	83	34	66
Hayashi et al., 2011	130	68	45	55	#	#	#	8.2	3.2	80	66	20
Regis et al., 2015	497	68.3	45.3	54.7	53.7	46.3	0	#	5	91.7	64.9	34.4

GKS (Gamma-Knife Surgery), NP (number of patients), R (right), L (left), Bil (bilateral), DOS (duration of symptons), y (years), APR (acute pain relief), PFR (pain-free rate), # (not clear)

Table 5. Demographic of patients and pain relief data of IN serie

References	NP	Age (y)	Male (%)	Female (%)	R (%)	L (%)	Bil. (%)	DOS (y)	Average FU (y)	APR rate (%)	Follow-up PFR (%)	Recurrence or failure rate (%)
Ko et al., 2015	26	46.9	7	20	12	14	0	#	3.6	85	72	27

IN (Internal Neurolysis), NP (number of patients), R (right), L (left), Bil (bilateral), DOS (duration of symptons), y (years), APR (acute pain relief), PFR (pain-free rate), # (not clear)

Table 6. Demographic of patients and pain relief data of MVD series

References	NP	Age (y)	Male (%)	Female (%)	R (%)	L (%)	Bil. (%)	DOS (y)	Average FU (y)	APR rate (%)	Follow-up PFR (%)	Recurrence or failure rate (%)
Klun et al., 1992	178	#	#	#	#	#	#	#	5.2	94	84	6
Zakrzewska and Thomas, 1993	65	54	40	60	59	39	2	#	5	#	62	38
Sun et al. 1994	61	64.4	33	67	54	46	0	7.5	6.6	#	82	18
Walchenbach et al., 1994	58	55.5	32.2	67.8	55.2	43.1	1.7	#	6.4	80	71	29
Mendoza and Illingworth, 1995	60	55.9	60	40	55.6	43.6	0.8	7.2	7.5	#	71	18
Barker et al., 1996	1155	57	40	60	61	37	2	6	6.2	98	70	30
Lee et al., 1997	146	#	#	#	#	#	#	#	5.7	96.5	89	8.6
Broggi et al., 2000	146	56	48.6	51.4	55.5	44.5	0	8.5	3.2	85	74	15.6
Tronnier et al., 2001	225	#	#	#	#	#	#	#	10.9	#	65	#
Tyler-Kabara et al., 2002	1188	55	39	61	50	37.5	12.5	#	5	98.2	80.5	19.5
Olson et al. 2005	156	65	33	67	58	42	0	#	10	93	74	18
Zakrzewska et al., 2005	220	59	59.5	40.5	#	#	#	6.7	5.3	89	84	4
Pamir and Peker, 2006	90	59	46.7	53.3	56	44	0	7	5	85.5	63	15
Sindou et al., 2006	362	61	47.5	52.5	61.9	38.1	0	6.4	8	86	80	15.1
Lagmari et al., 2007	51	50	62.8	37.2	57	43	0	3.9	7.3	94	77	15.6
Miller et al., 2009	67	54.3	38	62	56	44	0	5	3	#	84	16
Bond et al., 2010	119	60	51	49	66	34	0	#	3.3	91	81	10
Sarsam et al., 2010	266	59	38	62	54	41.6	4.4	6.7	7	98	71	29
Oesman and Mooij, 2011	156	58	42	58	65.5	34.5	0	7.3	9.7	88	82	18
Zhang et al., 2012	154	48	36	64	#	#	#	7	5.6	84	72	24
Sandel and Eide, 2013	226	63.1	40.3	59.7	53.9	46.1	0	7.3	6	85	83	12.4

MVD (Microvascular Decompression), NP (number of patients), R (right), L (left), Bil (bilateral), DOS (duration of symptons), y (years), APR (acute pain relief), PFR (pain-free rate), # (not clear)

Table 7. Reported complications related to RFT series

References	NP	Mortality	Hearing loss	Cerebellar oedeme or haematoma	Facial hypo or paresthesias	Corneal hypoesthesia	Trigeminal motor weakness	Anaesthesia dolorosa	Keratitis	Cranial nerve palsy	CSF leak	Meningitis	Herpes labial
Broggi et al., 1990	1000	0			52	197	105	15	6	5	1		
Taha and Tew, 1996	500												
Oturai et al., 1996	185												
Yoon et al., 1999	81	0	1		20	12	3		2				
Kanpolat et al., 2001	1600	0			16	91	66	12	10	14	2	1	
Huang et al., 2010	30	0			25		15	2	8				
Tang et al., 2015	1137	0	5		740		91		29	17	2		

RFT (Radiofrequency Thermocoagulation), NP (number of patients)

Table 8. Reported complications related to GR series

References	NP	Mortality	Hearing loss	Cerebellar oedeme or haematoma	Facial hypo or paresthesias	Corneal hypoesthesia	Trigeminal motor weakness	Anaesthesia dolorosa	Keratitis	Cranial nerve palsy	CSF leak	Meningitis	Herpes labial
Fujimaki et al., 1990	122	0			50			2					
Steiger, 1991	122	0	1		65	19	5			1			
Oturai et al., 1996	45												

GR (Glycerol Rhizotomy), NP (number of patients)

Table 9. Reported complications related to PBC series

References	NP	Mortality	Hearing loss	Cerebellar oedeme or haematoma	Facial hypo or paresthesias	Corneal hypoesthesia	Trigeminal motor weakness	Anaesthesia dolorosa	Keratitis	Cranial nerve palsy	CSF leak	Meningitis	Herpes labial
Lichtor and Mullan, 1990	61	0			8					1			
Skirving and Dan, 2001	496	0			42		17			8			
Omeis et al., 2008	29	0			16	1	2	1					
Campos and Linhares, 2011	39	0			4	1	7		1	1			
Chen et al., 2011	130				40	3	8			2		43	

PBC (Percutaneous Balloon Compression), NP (number of patients)

Table 10. Reported complications related to GKS series

References	NP	Mor-tality	Hea-ring loss	Cerebellar oedeme or haematoma	Facial hypo or pares-thesias	Corneal hypoes-thesia	Trige-minal motor weak-ness	Anaes-thesia doloro-sa	Kera-titis	Cranial nerve palsy	CSF leak	Menin-gitis	Herpes labial
McNatt et al., 2005	49	0			13				3				
Urgosik et al., 2005	107	0			21								
Longhi et al., 2007	160	0			14								
Dhople et al., 2009	112	0			6								
Han et al., 2009	60	0			8					2			
Riesenburger et al., 2010	53	0			19								
Hayashi et al., 2011	130	0			31								
Regis et al., 2015	497	0			72								

GKS (Gamma-Knife Surgery), NP (number of patients)

Table 11. Reported complications related to IN serie

References	NP	Mor-tality	Hea-ring loss	Cerebellar oedeme or haematoma	Facial hypo or pares-thesias	Corneal hypoes-thesia	Trige-minal motor weak-ness	Anaes-thesia doloro-sa	Kera-titis	Cranial nerve palsy	CSF leak	Menin-gitis	Herpes labial
Ko et al., 2015	26				25			1		1			

IN (Internal Neurolysis), NP (number of patients)

Table 12. Reported complications related to MVD series

References	NP	Mor-tality	Hea-ring loss	Cerebellar oedeme or haematoma	Facial hypo or pares-thesias	Corneal hypoes-thesia	Trige-minal motor weak-ness	Anaes-thesia doloro-sa	Kera-titis	Cranial nerve palsy	CSF leak	Menin-gitis	Herpes labial
Klun et al., 1992	178	3	1			1				2			
Zakrzewska and Thomas, 1993	65	0	3										
Sun et al. 1994	61	0	1		7					4			6
Walchenbach et al., 1994	58	0		2	2								
Mendoza and Illingworth, 1995	60	1		1	3					8	2	1	
Barker et al., 1996	1155	2	15	6	11					21	17	4	
Lee et al., 1997	146												
Broggi et al., 2000	146	0	8	1	3					6	12		
Tronnier et al., 2001	225	2	17	2	28						2		7
Tyler-Kabara et al., 2002	1188	4		12						156	33	5	
Olson et al. 2005	156	0	1	2				1			7	4	
Zakrzewska et al., 2005	220	0	24		19	10							
Pamir and Peker, 2006	90	0		1	1					1	1		
Sindou et al., 2006	362	2	7	1	11					6			
Lagmari et al., 2007	51	0	2		12					2		4	
Miller et al., 2009	67												
Bond et al., 2010	119	0								2	1		
Sarsam et al., 2010	266	0	5		26					5	20		
Oesman and Mooij, 2011	156	0	4	1	13	3				4	1	1	3
Zhang et al., 2012	154	0	1		8	3							
Sandel and Eide, 2013	226	1	6	3	2						7	1	

MVD (Microvascular Decompression), NP (number of patients)