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Microvascular Decompression VS Gamma Knife Surgery for the Surgical Management of Trigeminal Neuralgia

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Abstract: - **Background: Trigeminal neuralgia (TN) is a rare chronic facial pain syndrome, characterised by severe, stabbing pain felt in one or more divisions of trigeminal nerve innervation areas. TN pain is so excruciating that it heavily impacts a patient's quality of life.**

Most cases can be controlled using anti-convulsive medications, however some patients do not respond to medication or have adverse effects to them at which point surgery is considered. Many different surgical procedures are available for TN, however Microvascular Decompression (MVD) and Gamma Knife Surgery (GKS) are amongst the most widely used. This appraisal seeks to determine whether MVD is more successful than GKS in treating TN.

Method: Medline, Embase and The Cochrane Database of Systematic Reviews were searched, as well as executing a hand search of Google, for relevant studies comparing pain relief, pain recurrence and complications of MVD & GKS. Studies must have been published in the last 5 years, must have measured pain using the Barrow Neurological Institute (BNI) pain scale and patient follow-up must have been at least one-year post-surgery. This resulted in 2 studies meeting the inclusion criteria, which were then selected for appraisal.

Results: Both studies showed a statistically significant difference between the effectiveness of MVD and GKS in the management of TN. However, both studies had several flaws, weaknesses and were subject to bias, thus impacting on their credibility.

Conclusion: Whilst the evidence suggests MVD provides superior outcomes than GKS, further research is required in the form of a Randomised Controlled Trial to categorically determine which treatment is more effective.

INTRODUCTION

Clinical Scenario

A patient attends your dental surgery for a regular check-up and looks extremely distressed and on the verge of tears. Upon comforting her, she explains that her Trigeminal Neuralgia is no longer responding to the medication prescribed by her GP.

You have been treating the patient ever since you started working at this practice and you have seen how Trigeminal Neuralgia has been affecting her and her quality of life. She explains that she is living in fear of the thought of having another episode, knowing that her medication is futile. She is otherwise fit and well and is very keen on the idea of surgical treatment. She knows that there are many different surgical procedures to treat the condition but doesn't know much about them. The patient explains that upon ringing her local hospital, she discovered that they offer two surgical treatments for Trigeminal Neuralgia: 'Microvascular Decompression' and 'Gamma Knife Surgery'.

As a dental surgeon, she perceives you as someone who is knowledgeable about conditions affecting the facial area and asks for your advice on which procedure would be the most successful in treating her Trigeminal Neuralgia. You are keen to provide the patient evidence-based advice and therefore begin examining the literature.

Introduction

The Trigeminal Nerve

The Trigeminal Nerve [**V**] (Figure 1) is the 5th cranial nerve and is considered the main sensory nerve of the head and also innervates the muscles of mastication.

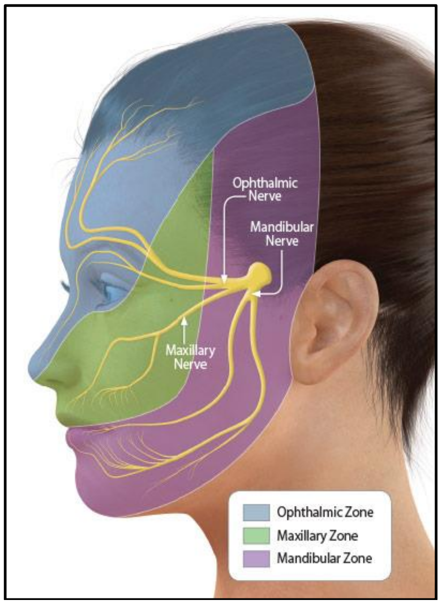


Figure 1: Divisions of The Trigeminal Nerve (Source: Dear Doctor Dentistry & Oral Health, 2015)

It consists of 3 divisions:

Opthalmic [V1]:

This branch provides sensation to the eyes, upper eyelid, anterior part of the scalp, conjunctiva, orbital contents, lacrimal gland, nasal cavity, dorsum of the nose, and the anterior part of the scalp.

Maxillary [V2]:

This branch provides sensation to the upper lip, teeth of the upper jaw, the palate, the lower eyelid, the cheek, the nasopharynx, the nasal cavity, and skin covering the side of the nose.

Mandibular [V3]:

The mandibular division leaves the skull via the foramen ovale and is the only branch that contains motor fibres and provides motor innervation to the 4 muscles of mastication; masseter, temporalis & the medial and lateral pterygoids. It also provides sensory innervation to the teeth of the lower jaw, lower lip, skin of the lower face, cheek, the mandible, anterior part of the external ear, part of the external acoustic meatus, the temporal region, the anterior two-thirds of the tongue & the mucous membranes of the cheek.

The trigeminal ganglion contains the cell bodies for the sensory neurons and is found in a depression (the trigeminal depression) on the anterior surface of the petrous part of the temporal bone in the middle cranial fossa (Drake, Vogl and Mitchell, 2009).

Trigeminal Neuralgia

Trigeminal Neuralgia (TN) or *Tic Douloureux* is an agonisingly painful disease that is categorised by abrupt episodes of severe lancinating (stabbing) pain in one or more divisions of the trigeminal nerve. (Samandouras, 2010)

Prevalence & Epidemiology

The prevalence of this condition has been reported to be 27 per 100,000 of the population (Ghurye and McMillan, 2017), and it is well known that the condition is twice as common in females than males (Jurge, 2016). TN is most commonly seen in people between 50-70 years of age (Grant and Loeser, 2012).

Aetiology

TN is the result of damage to the trigeminal nerve myelin sheath & is of two types according to the latest International Headache Society (IHS) Classification:

2. **Classical Trigeminal Neuralgia (also known as Primary TN)**: Where there is no other apparent cause for TN except neurovascular compression.
2. **Painful Trigeminal Neuropathy (previously known as Symptomatic TN):** Where TN is caused by a disorder other than neurovascular decompression e.g. Multiple Sclerosis, tumours, infections, cysts and trauma (International Headache Society, 2013).

In most cases, TN is of the classical type and occurs due to the compression of the trigeminal nerve at the root entry zone which in turn causes damage to the myelin sheath and demyelination of the nerve (Hupp, 2008).
The damage to the myelin sheath and demyelination causes the neurones to become hyperactive resulting in the autonomous firing of impulses in atypical locations, which results in the characteristic sudden severe bouts of pain. In most cases, the compression of the nerve root is due to the superior cerebellar artery or vein (Jurge, 2016).

Clinical Features & Symptoms

The clinical features of TN include:

A sudden 'electric shock' like shooting pain lasting from a few seconds to less than 2 minutes
Recurrent and intermittent pain usually with complete relief between episodes
Mostly Unilateral
Severe intensity of pain
Triggered by stimulating the trigeminal trigger zones (Figure 2) by factors such as a gentle breeze, brushing teeth, shaving, chewing or even speaking
Can be mistaken for tooth ache

Table 1: Clinical features and symptoms of TN

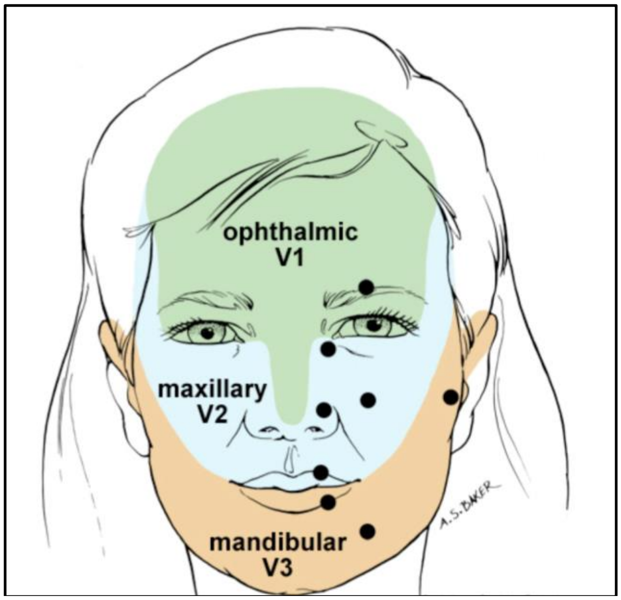


Figure 2: Facial area of Trigeminal Nerve trigger zones. Circles indicate trigger points of greatest sensitivity (Source: Mayfield Brain & Spine, 2016)

The maxillary division [V2] is more commonly affected followed by the mandibular [V3]. The ophthalmic division [V1] is rarely affected. Most patients are usually only affected in one division but over time other divisions can become involved (Scully *et al.*, 2010).

Diagnosis

Detailed pain and medical histories are crucial in the diagnosis of TN. A cranial nerve examination is also important for differential diagnosis (Jurge, 2016).

Magnetic Resonance Image (MRI) scans are usually performed on all patients with symptoms as it can determine the underlying cause of the TN (Figure 3) such as Multiple Sclerosis plaques, tumours and blood vessels which may be compressing the trigeminal nerve (Ghurye and McMillan, 2017).

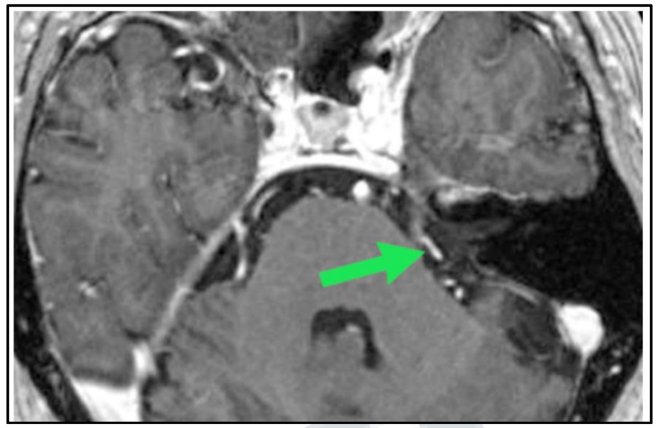


Figure 3: MRI scan showing a blood vessel (arrow) compressing the trigeminal nerve (Source: Mayfield Brain & Spine, 2016)

Prognosis

At least 50% of people with TN have remissions lasting at least 6 months. TN becomes more severe and less responsive to treatment over time, despite increasing medication dose and the use of additional agents. Most people with TN are initially managed medically, and a proportion eventually have a surgical procedure. It is also indicated that pain relief is better after surgery than with medical treatment (Zakrzewska & Linskey, 2013).

Treatment

Pharmacological:

Initial treatment for TN is achieved using anti-convulsive medication. Drugs including Carbamazepine, Gabapentin & Phenytoin all demonstrate reducing and controlling TN pain (Grant and Loeser, 2012).

The National Institute for Health and Clinical Excellence (NICE) recommend Carbamazepine as the first line drug for TN. An initial dose of 100mg twice daily should be given and then increased by 100-200mg every fortnight until the pain is relieved. Once the patient is in remission, the dose should be reduced gradually to the lowest possible maintenance level (NICE, 2017).

Surgical:

Surgical interventions for TN are to be considered if sufficient pain control cannot be achieved by the use of medication or if the patient has adverse side effects to it. Once this has been established, referral to a specialist should not be delayed (NICE, 2017).

Procedure	Description
Peripheral procedures	These interventions involve the destruction or blocking of portions of the trigeminal nerve distal to the Trigeminal (Gasserian) ganglion. These include; neurectomy, cryotherapy, alcohol or phenol injections, radiofrequency thermocoagulation where the portions of the nerve are destroyed using heat, or peripheral acupuncture (Jurge, 2016).
Gasserian Ganglion Procedures	These interventions involve penetration of the foramen ovale with a cannula and then damaging the trigeminal ganglion by various means: **Thermal** by means of radiofrequency thermocoagulation, **chemical** by means of injection of glycerol or **mechanical** by means of compression by a balloon inflated into the trigeminal cave (Cruccu *et al.*, 2008).
Intracranial Procedures	These interventions focus on the trigeminal root in the posterior fossa of the skull and consist of 2 main procedures, **Microvascular Decompression (MVD)** and **Gamma Knife Surgery (GKS)** both of which will be discussed below and are the main concern of this appraisal (Jurge, 2016).

Table 2: Surgical Procedures for TN

Surgical procedures for TN can be categorised into 3 groups:

Microvascular Decompression (MVD)

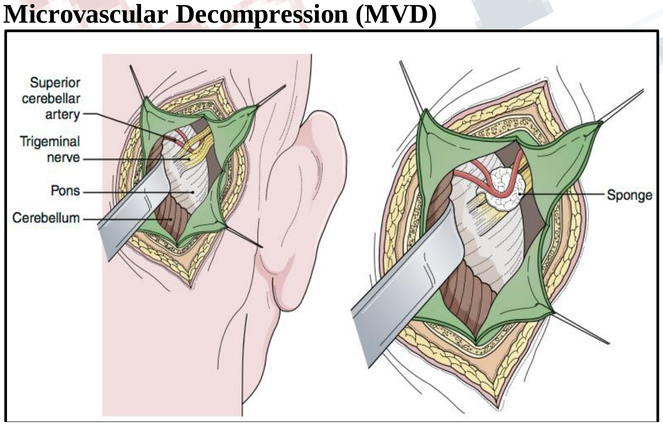


Figure 4: MVD showing the site of craniotomy & sponge being inserted between the trigeminal nerve and the compressing blood vessel (Source: Grant and Loeser, 2012)

MVD is a major neurological procedure, however this procedure aims to preserve the trigeminal nerve. Due to its invasive nature, it is more frequently the treatment of choice in younger, healthier patients & is usually carried out when the cause of TN is due to nerve compression.

MVD involves creating an opening through the skull (craniotomy) in the lateral posterior fossa behind the ear. Retractors are then gently placed on the brain exposing the trigeminal nerve at its root. The responsible blood vessel is then identified and separated from the nerve and material such as Teflon or synthetic sponge is inserted to maintain the separation and protect the nerve as shown in Figure 4 (Grant and Loeser, 2012).

Gamma Knife Surgery (GKS)

Gamma Knife Surgery is a type of stereotactic radiosurgery invented by Swedish neurosurgeon, Professor Lars Leksell (The National Centre for Stereotactic Radiosurgery, 2014). It uses high-energy intersecting beams of ionising radiation to destroy some of the fibres of the trigeminal nerve (Mayfield Brain & Spine, 2016). It is a non-invasive procedure and is therefore indicated in patients who are unable to undergo more invasive surgical techniques. (The National Centre for Stereotactic Radiosurgery, 2014).

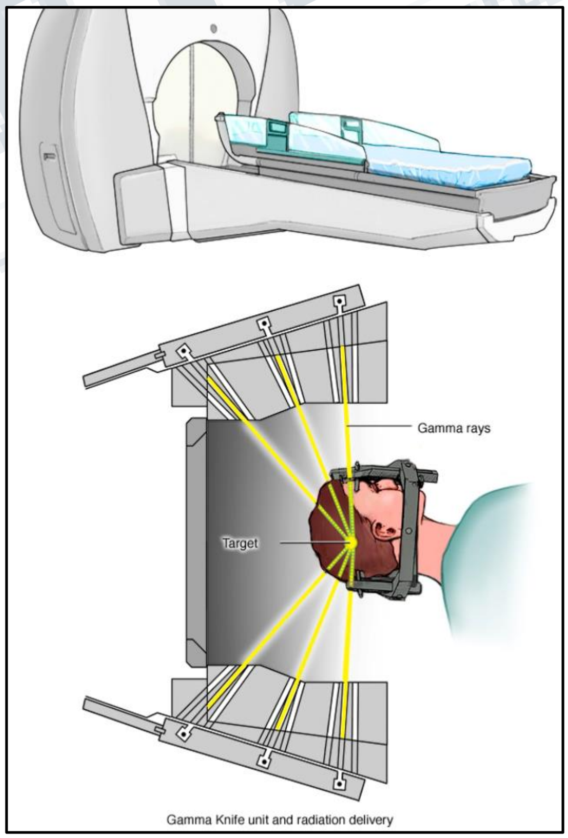


Figure 5: Leksell gamma knife unit & delivery of radiation (Source: Mayo Clinic, 2016)

The resulting damage to the trigeminal nerve prevents pain signals from travelling to the brain and thus aims to eradicate the pain associated with TN.

A stereotactic head frame or facemask is attached to the patient's head (Figure 5) to precisely locate the nerve on an MRI scan so that the high-energy beams of gamma radiation can be delivered to the trigeminal nerve root. The head frame also helps to keep the patient's head stationary (Mayfield Brain & Spine, 2016). Doses of radiation usually ranging from 60-90 Gy are usually administered (Grant and Loeser, 2012).

Importance of the Topic to Clinical Practice
TN can affect a wide range of patients of all ages meaning that some of these patients will be healthier and fitter than others (Ghurye and McMillan, 2017). As mentioned previously, MVD is an invasive procedure unlike GKS and may not be suitable for elderly patients or those with more complex medical histories (Grant and Loeser, 2012). Therefore, it is important to identify and appraise studies which look at and analyse the success of MVD and GKS, including complications, so that the dental practitioner can advise patients on which surgery may be best for them, based on their medical history and general health. The dental practitioner should have adequate records of each patient, thus allowing them to provide evidence-based, tailored advice for each patient.

Not only this but patients with TN may have poorer oral health as they are more reluctant to visit the dentist for dental treatment or even brush their teeth as these can be triggers of TN (Brisman, 2017). Consequently, it is necessary to review the literature to determine which of MVD or GKS will be more successful in treating TN and provide long-lasting pain relief. The procedure which provides the most substantial pain relief & with least recurrence will in turn, provide the greatest improvement to a patient's quality of life, all three of which will motivate and lead to the patient improving their oral health.

I. RESEARCH QUESTION

'Is Microvascular Decompression more effective than Gamma Knife Surgery for the surgical management of Trigeminal Neuralgia'

To formulate an effective research question, the following PICO format was used:

Population of Interest: Adults (18+) with Classical Trigeminal Neuralgia affecting one or more branches of the trigeminal nerve

Intervention: Microvascular Decompression

Comparison: Gamma Knife Surgery

Outcomes of Interest:

- Primary:
  - Pain Relief (measured using the 'Barrow Neurological Institute (BNI) Pain Scale')
  - Pain Recurrence
- Secondary
  - Complications (e.g. numbness)

Table 3: PICO format

II. IDENTIFICATION OF STUDIES

The following central concepts were identified:

- Trigeminal Neuralgia
- Microvascular decompression
- Gamma Knife Surgery, Radiosurgery and Stereotactic
- Barrow Neurological Institute Pain Scale (BNI)

Thereafter, the following databases were searched using both free text and MeSH terms:

MEDLINE (Ovid) 1946 to December Week 2 2017

Number	Searches	Results
1	Trigeminal Neuralgia/ or Trigeminal Neuralgia.mp.	7573
2	Tic douloureux.mp.	287
3	TN.mp.	10359
4	1 or 2 or 3	17209
5	Microvascular Decompression.mp. or Microvascular Decompression Surgery/	1580
6	Microsurgery.mp. or Microsurgery/	30485
7	MVD.mp.	4873
8	Jannetta.mp.	60
9	5 or 6 or 7 or 8	36021
10	Gamma Knife.mp. or Radiosurgery/	14894
11	Stereotactic.mp.	20189
12	GKS.mp.	796
13	10 or 11 or 12	26482
14	Barrow Neurological.mp. or Treatment Outcome/ or Pain Measurement/	986230
15	BNI.mp.	981
16	14 or 15	987014

17	4 and 9 and 13 and 16	82
18	Limit 17 to English Language, Humans and Year = "2012-Current"	28

Embase (Ovid) 1974 to 2017 Week 52

Number	Searches	Results
1	Trigeminal Neuralgia.mp. or Trigeminus Neuralgia/	10867
2	Tic douloureux.mp.	310
3	TN.mp.	15713
4	1 or 2 or 3	25470
5	Microvascular Decompression.mp. or Microvascular Surgery/ or Microvascular Decompression/ or Decompression Surgery/ or Microsurgery/	48948
6	Jannetta.mp.	76
7	MVD.mp.	7276
8	5 or 6 or 7	55458
9	Gamma Knife.mp. or Stereotaxic Surgery/ or Gamma Knife/	20844
10	Radiosurgery.mp. or Radiosurgery/ or Gamma knife Radiosurgery/	23952
11	Stereotactic.mp. or Stereotactic Radiosurgery/	40513
12	GKS.mp.	1070
13	9 and 10 and 11 and 12	58430
14	Barrow Neurological Inst*.mp.	339
15	BNI.mp.	1281
16	14 or 15	1485
17	4 and 8 and 13 and 16	45
18	Limit 17 to English Language, Humans and Year = "2012-Current"	30

The Cochrane Database of Systematic Reviews (Ovid) 2005 to January 2018

Number	Searches	Results
1	Trigeminal Neuralgia.mp.	61
2	Tic douloureux.mp.	1
3	TN.mp.	180
4	1 or 2 or 3	238
5	Microvascular Decompression.mp.	5
6	Microsurgery.mp.	18
7	MVD.mp.	31
8	Jannetta.mp.	0
9	5 or 6 or 7 or 8	52
10	Gamma Knife.mp.	11
11	Radiosurgery.mp.	23
12	Stereotactic	35
13	GKS.mp.	3
14	10 or 11 or 12 or 13	45
15	4 and 9 and 14	1

A hand search using the Google search engine was also conducted however no relevant studies were identified.
As part of the search strategy, a limit was not placed on the study type due to the sheer lack of Randomised Controlled Trials and high-ranking studies on the evidence hierarchy for the chosen research question.

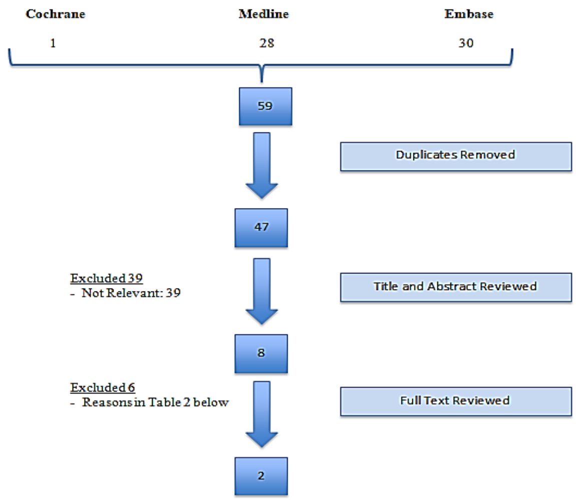
III. SEARCH RESULTS & INCLUSION CRITERIA

The inclusion criteria for the searches were as follows:

- Studies must compare MVD and GKS based on the above-mentioned outcomes
- Patients must have Classical Trigeminal Neuralgia
- Patient follow up must be at least one-year post-surgery
- Studies must have been published in the last 5 years
- Studies must measure pain relief using the Barrow Neurological Institute (BNI) pain scale

Short-term surgical outcomes can vary significantly from the long-term outcomes and may not be a true & accurate representation on the effectiveness of either procedure. For this reason, the criteria of a one-year or longer post-surgery follow-up was implemented.
The reason studies published in the last 5 years are being used only, is due to the fact that MVD and GKS are relatively contemporary procedures. There have been many recent advancements in both procedures which have improved the results of surgeries, such as endoscopes being used to assist MVD as well as new materials being used for padding (Casey, 2017). Not only this but improvements in better defining the optimal target in GKS have also enhanced surgical results, to name but a few (Montano *et al.*, 2015).
The BNI pain scale is being used as it was specifically developed for Trigeminal Neuralgia and is therefore more standardised and much less subjective than other pain scales (Rogers *et al.*, 2000). Unlike other single faceted pain scales, the BNI pain scale not only takes into account pain intensity but also the level of medication used for pain (Kumar *et al.*, 2013).

Below is a flowchart of the search results:



Of the studies found, 2 met the inclusion criteria:

- Inoue, T. *et al.* (2017). Long-term outcomes of microvascular decompression and Gamma Knife surgery for trigeminal neuralgia: a retrospective comparison study, *The European Journal of Neurosurgery*, 159(11), pp.2127-2135
- Dai, Z. *et al.* (2016). Efficacy of stereotactic gamma knife surgery and microvascular decompression in the treatment of primary trigeminal neuralgia: a retrospective study of 220 cases from a single center, *Journal of Pain Research*, 2016(9), pp.535-542

Thus, the above 2 studies were selected for appraisal.

The following articles were rejected after the full text was reviewed:

Study	Reasons for rejection
Zakrzewska, J.M. and Akram, H. (2011)	- Does not assess MVD as no Randomised Controlled Trials existed for it - Study is over 5 years old, published in 2011
Nanda, A. *et al.* (2015)	- Does not assess complications *
Kang, I.H. *et al.* (2016)	- Only assesses MVD, no patients underwent GKS
Rzaev, J. (2017)	- Includes patients with non-classical TN - Compares MVD to Stereotactic radiosurgery as a whole ** - Cannot access full text
Inoue, T. *et al.* (2017)***	- Only assesses MVD, no patients underwent GKS
Gubian, A. *et al.* (2017	- Compares MVD to Stereotactic radiosurgery as a whole. Unable to distinguish whether GKS was used

Table 4: Rejected studies from the databases after reviewing full text & after duplicate studies were removed

*Although complications are a secondary outcome, the study by Nanda, A. *et al.* (2015) is being rejected as complications can heavily define and determine the success of surgery. If MVD or GKS lead to numbness, paralysis or hearing loss for example, then this will significantly impact the patient's quality of life and the surgery cannot be considered successful despite pain relief. Since this study does not include complications, it is being rejected for the aforementioned reasons.

**It should be noted that the 2 studies that are being rejected due to them looking at stereotactic radiosurgery as a whole, are due to the fact gamma knife is one type of stereotactic radiosurgery. These 2 studies look at other types of stereotactic radiosurgery also such as cyber knife surgery and the results cannot be separated and it cannot be distinguished whether GKS has been used by analysing the results.

***It is also to be noted, that the study by Inoue, T. *et al.* (2017) that is being rejected is not the same study by Inoue, T. *et al.* (2017) that is being accepted.

IV. CRITICAL APPRAISAL

Study	Inoue, T. *et al.* (2017) Long-term outcomes of microvascular decompression and Gamma Knife surgery for trigeminal neuralgia: a retrospective comparison study *The European Journal of Neurosurgery,* *Volume 159 Issue 11* *pp. 2127-2135*
Patient Group	A total of **231** patients were included, 179 underwent Microvascular Decompression (MVD) and 52 underwent Gamma Knife Surgery (GKS) In the MVD group:

	• 65 males & 114 females were treated • Mean age was 62 years • Age range was 19-97 years In the GKS group: • 17 males and 35 females were treated • Mean age was 72 years • Age range was 45-89 years Inclusion Criteria • Must be the initial surgical treatment patients undergo • Patients must have Classical/Typical Trigeminal Neuralgia Exclusion Criteria • Patients with Non-Typical (symptomatic) Trigeminal Neuralgia • Patients who had undergone previous surgery for Trigeminal Neuralgia • Patients where follow-up was less than 1-year post-surgery
Intervention	Pre-surgery, to identify any vascular involvement and exclude any implication of tumours, all patients underwent two sequences of magnetic resonance imaging (MRI). In the MVD Group: • CT scans of the craniotomy site and 3D images using GammaPlan® (ELEKTA, Stockholm, Sweden) were taken to determine the anatomical relations between the nerve and vessels • MVD was performed with the retrosigmoid approach under general anaesthesia. In the GKS Group • CT scans with bone window levels were performed to detect and correct the distortion of MRI and determine the accurate target • A Leksell head frame was firmly fixed to the patient's head under local anaesthesia • GammaPlan® was used to accurately determine the target by the patient's CT and MR images • Irradiation was performed with a single isocenter at the maximum dose of 85–92 Gy (median, 88 Gy) via a 4-mm collimator helmet.
Outcomes Assessed	Interviews were conducted with patients to assess **pain relief, complications and recurrence** Interviews were conducted at least 1-year post-surgery, with a median of 3.3 years and a range of 1 to 11.1 years. Pain relief was measured using the BNI pain score pain intensity score (P). The scale was used in the following way; **P-1=** No pain & No medication, **P-2=** Occasional pain, not requiring medication, **P-3=** Some pain, adequately controlled using medication**,** **P-4=** Some pain, not adequately controlled using medication & **P-5=** Severe pain/No relief Numbness was measured using the BNI facial numbness score (N); **N-1=** No facial numbness, **N-2=** Mild facial numbness, not bothersome, **N-3=** Facial numbness, somewhat bothersome, **N-4=** Facial numbness, very bothersome. The total of both scores (T = P + N) was defined as **excellent (T: 2)**, **good (T: 3), fair (T: 4)** or **poor (*T* ≥ 5)** 'Recurrence' was defined as any degree of recurrent pain requiring medication and/or additional surgical procedures after reaching a medication-free status (BNI P3 or higher) Complications other than facial numbness were documented separately.
Key Results	Data was analysed using two-tailed Fisher exact tests for nominal data and Student's t-tests for continuous data. A *P*-value less than 0.05 was considered statistically significant. P-values were determined using Pearson's X^2 test **Pain Relief** In the MVD group, 144 patients (80.4%) were graded P-1 (no pain, no medication), 17 (9.5%) were graded P-2 (occasional pain, not requiring medication), 15 (8.4%) were graded P-3 (some pain, adequately controlled with medication), and 3 (1.7%) were graded P-4/5 (some pain, not adequately controlled with medication/severe pain/no pain relief). In the GKS group, the number of patients graded P-1, P-2, P-3 and P-4/5 was 20 (38.5%), 3 (5.8%), 12 (23.1%) and 17 (32.7%), respectively. The groups statistically differed from each other ($P < 0.001$), suggesting greater pain relief was achieved following MVD than following GKS. **Numbness**

	In the MVD group, 144 patients (80.4%) were graded N-1 (no facial numbness), 25 (14.0%) were graded N-2 (mild facial numbness, not bothersome), and 10 (5.6%) were graded N-3/4 (facial numbness, somewhat bothersome/very bothersome). In the GKS group, the number of patients graded N-1, N-2 and N-3/4 was 33 (63.5%), 13 (25.0%) and 6 (11.5%), respectively. The groups differed significantly from each other ($P = 0.04$), suggesting patients undergoing GKS more frequently experienced postoperative numbness than did those undergoing MVD. **Recurrence** Recurrence (≥ P-3) over time was found in 11 patients (6.1%) undergoing MVD and 27 patients (51.9%) undergoing GKS ($P < 0.001$). **Other Complications** Aside from numbness, severe dry eye requiring periodical care by ophthalmology was found in both groups at the final assessment. However, hearing disturbance (dysfunction of the eighth nerve), masticatory weakness (dysfunction of trigeminal motor root) and cerebellar dysfunction were only noted in the MVD group. However, there were no significant differences between the groups for rates of complications besides facial numbness. **Overall Outcome** The overall outcome at the final follow-up was evaluated by summing the BNI pain intensity score and the BNI facial numbness score In the MVD group, 122 patients (68.2%) were graded "excellent," 28 patients (15.6%) "good," 19 patients (10.6%) "fair" and 10 patients (5.6%) "poor." In the GKS group, 13 patients (25.0%) were graded "excellent," 5 patients (9.6%) "good," 11 patients (21.2%) "fair" and 23 patients (44.2%) "poor." As such, MVD provides a significantly superior long-term outcome compared with GKS ($P < 0.001$)
Study Type Including: Strengths (✓) Weaknesses (✘) Potential Bias (✘)	**Retrospective Cohort Study** ✓ Clearly displayed results ✓ Patient gender, mean age as well as range included ✓ The affected branches of the TN nerve as well as the offending vessel included for each patient ✓ Patients had no prior surgery to treat TN ✓ Range and median follow up years included for both groups ✓ Rigorous pre-op assessment for each patient to exclude diseases and ensure surgeries are effective ✓ Combines Pain and Numbness scores to form separate score ✓ P-values were determined using Pearson's X^2 test ✓ P-Value of <0.05 set as being statistically significant ✓ Two-tailed Fisher exact & Student's t-tests used ✓ Pain-free period without medication after treatment determined using Kaplan-Meier analysis ✓ The maximum median radiation dose (88 Gy) was used and was within the recommended dosage ✓ Analysis of the data was conducted with commercially available software (JMP®, SAS, Cary, NC, USA) ✘ Small patient sample (231 patients) ✘ Patients were not randomly allocated to the treatments ✘ Patients chose their own surgery therefore their choice was subject to bias ✘ Not stated whether patients have any other health conditions ✘ Patients were treated from 2005 to 2016 during which surgical techniques and technology, standards & policies to name but a few may have drastically changed ✘ All treatments were carried out at a single centre only therefore less generalizable results ✘ Cannot exclude the possibility that differences observed in the study may have been caused by differences in baseline characteristics between the two groups ✘ Relatively large difference in male:female ratio ✘ Large difference in time between surgery and follow up (range, 1–11.1 years) ✘ Not an equal number of patients for the intervention and comparison (179 and 52 respectively)

	✖ Very large age difference between patients (19-97 for MVD & 45-89 for GKS) ✖ No mention of what material was used for nerve-vessel separation in MVD ✖ No power calculation ✖ No confidence intervals ✖ Not stated whether more than one different surgeon undertook the procedures ✖ A limit was not placed on the period from pain onset to treatment (0.1 to 40 years in MVD group and 0.5 to 24 years in GKS group) ✖ No details of funding

Study	Dai, Z. *et al.* (2016) Efficacy of stereotactic gamma knife surgery and microvascular decompression in the treatment of primary trigeminal neuralgia: a retrospective study of 220 cases from a single center *Journal of Pain Research* *Volume 2016 Issue 9* *pp.535-542*
Patient Group	A total of **202** patients were included, 87 underwent Microvascular Decompression (MVD) and 115 underwent Gamma Knife Surgery (GKS) In the MVD group: • 52 females & 35 males were treated • Mean age 58±11.6 • Age range was 36-77 years In the GKS group: • 60 females & 55 males were treated • Mean age 63±10.7 years • Age range was 26-89 years All patients had Classical/Primary Trigeminal Neuralgia Inclusion criteria not reported Exclusion criteria not reported
Intervention	Pre-surgery, MRI Texture Analysis (MRTA) was performed in all the patients to exclude the presence of intracranial lesions, including neoplasms, and to confirm the neurovascular relationships. In the MVD Group • The Suboccipital Retrosigmoid sinus approach was used • MVD was assisted using a microscope • Teflon was used as the material to separate the vessel from the nerve • The Trigeminal Nerve (fifth), seventh, and eighth cranial nerves were monitored continuously by electromyography and brainstem auditory-evoked potentials In the GKS Group: • A Leksell model "G" frame was fixed to the patient's head under local anaesthesia. • Leksell gamma knife software (ELEKTA, Stockholm, Sweden) was used to acquire the radiosurgical target. • The treatment procedure was performed with two isocenters, where one target was the nearby Gasserian ganglion, and the other target was about 2−4 mm away from the brainstem, via a 4 mm collimator helmet that targeted the trigeminal nerve root entry zone. • The margin dose was 59.5 Gy, and a 70% isodose line enclosed the target margin in all patients, & a brainstem dose of <12 Gy.
Outcomes Assessed	Follow-up was conducted for all the patients via telephone or in the Outpatient Department to assess **pain relief**, **recurrence** and **complications.** Post treatment follow up occurred for 2 years. The BNI pain intensity scale was used as follows: **BNI I:** no pain, no medication; **BNI II**: occasional pain, not requiring medication; **BNI III:** some pain, adequately controlled with medication; **BNI IV:** some pain, not adequately controlled with medication; **BNI V**: severe pain or on pain relief. Operative complications were also recorded. Recurrence was checked at less than 6 months, 6-12 months & 12-24 months The Visual Analog Scale (VAS) was also used to assess pain relief.

Key Results	The independent samples *t*-test was used to analyse continuous data. The χ^2 test and the Mann−Whitney *U* test were used for comparing the categorical data. Statistical significance was assumed as $P<0.05$. **Pain Relief** Postoperative GKS and MVD BNI scores were both significantly improved compared with their respective preoperative BNI scores ($P<0.01$). After 2 years of follow-up, 102 patients (88.7%) treated with GKS attained pain relief (BNI pain score I−III), compared to 83 patients (95.4%) in the MVD group. 83% of MVD patients attained a BNI score of 1 compared with only 52% of GKS patients attaining a BNI score of 1 (P<0.01) There was, therefore, a significant difference in the total pain remission rate between GKS (88.7%) and MVD (95.4%), with $P<0.01$. Within 3 months after the operation, the pain remission rate of the GKS and MVD groups were significantly different ($P=0.004$) at 81.7% (n=94) and 95.4% (n=83), respectively. **Recurrence** Twelve GKS-treated patients (10.4%) experienced pain recurrence between 6 months and 2 years after the procedure where as 6 patients (6.9%) who underwent MVD experienced pain recurrence. The pain recurrence rates were not significantly different at different time points between patients treated with GKS and MVD ($P>0.05$). **Complications** Twenty-five patients (21.7%) treated with GKS had a significantly increased rate of loss of corneal reflex, compared with five patients (5.7%) treated with MVD ($P=0.002$). Twenty patients (17.3%) treated with GKS and 13 patients (14.9%) treated with MVD experienced facial numbness ($P=0.704$). Herpes zoster around the mouth (15 patients), facial paralysis (4 patients), and hearing loss (3 patients) were complications specific to MVD.
Study Type Including: Strengths (✓) Weaknesses (✗) Potential Bias (✗)	**Non-Randomised Clinical Trial** ✓ Patient gender, mean age as well as range included ✓ The independent samples *t*-test was used to analyse continuous data ✓ The χ^2 test and the Mann−Whitney *U* test were used for comparing the categorical data. ✓ P-Value of 0.05 set as being statistically significant ✓ The Visual Analog Scale (VAS) as well as the BNI pain scale were both used to assess pain relief ✓ The number of affected branches of the TN nerve as well as whether the offending vessel was a vein or artery included ✓ Binary logistic regression was performed to analyse how preoperative factors (sex, age, disease course, pain distribution, and VAS scores) influenced postoperative pain relief. ✓ Kaplan−Meier survival curves were used to analyse the relationship between pain relief and follow-up time ✓ Material used to separate nerve and vessel in MVD reported (Teflon) ✓ Pre-op assessment for each patient to exclude diseases and ensure surgeries are effective ✓ 95% confidence interval used ✓ Patients were assessed for recurrence on 3 separate occasions between 6 to 24 months ✓ Patients were followed up for the same length of time ✓ All patients were treated within very close of each other (January 2013 and December 2014) reducing the effects of technological or technical advancements/changes and policy and standard changes affecting results. ✗ Small patient sample (202 patients) ✗ Patients were not randomly allocated to the treatments ✗ Patients chose their own surgery therefore their choice was subject to bias ✗ Not stated whether patients have any other health conditions ✗ Not an equal number of patients for the intervention and comparison (87 and 115 respectively) ✗ A lower dose (59.5Gy) was used than the recommended dose for GKS ✗ Study does not state whether the surgeries conducted were first time surgical interventions for the patients or not

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	✗ All treatments were carried out at a single centre only therefore less generalizable results ✗ Inclusion and exclusion criteria not reported ✗ 'Recurrence' not defined ✗ No power calculation ✗ Not stated whether more than one different surgeon undertook the procedures ✗ A limit was not placed on the time period from pain onset to treatment ✗ No details of funding

V. SUMMARY & DISCUSSION

Setting

The two studies that have been appraised above have some similarities as well as many differences. Both Inoue, T. *et al.* (2017) and Dai, Z. *et al.* (2016) are mono-centred studies which is a weakness as the results may not be generalizable. Neither of the 2 studies state whether the procedures were carried out by a single surgeon or multiple surgeons, and this can affect the results as some surgeons may be more skilled at MVD over GKS and vice versa. Patients were not randomised in both studies and all patients were able to choose their own surgery which further weakens the two studies and leads to bias. If patients were randomised and the studies were multi-centred, this would have greatly enhanced the strength of the two studies.

Patients Included

Significant differences were noted in the patient population between the two studies. Inoue, T. *et al.* (2017) had 231 participants, of which 179 underwent MVD and 52 (GKS). Dai, Z. *et al.* (2016) on the other hand had fewer participants (202 patients) however there was a smaller difference in number between the two procedures **(**87 underwent MVD and 115 underwent GKS). Inoue, T. *et al.* (2017) also has a relatively larger difference in male:female ratio which may lead to potential bias.

Both studies included patients with Classical TN only, however where Inoue, T. *et al.* (2017) explicitly states this was the first surgery patients were undergoing for TN, Dai, Z. *et al.* (2016) does not mention whether this was the first surgical intervention that the patients had received. This could significantly weaken the study and may lead to huge bias as second-time surgery may have completely different outcomes to first time surgery. Not only this but Inoue, T. *et al.* (2017) has a clear exclusion and inclusion criteria where as Dai, Z. *et al.* (2016) does not report this and one must try to determine the criteria through analysis of the finer details of the study.

Intervention

The principal aim of both studies was to determine which of MVD or GKS is more successful in treating TN.

For MVD:

In both studies, patients underwent preoperative MRI scans to rule out tumours and other possible causes for TN which increases the strength of the studies. However, Inoue, T. *et al.* (2017) carried out two sequences of MRI scans as opposed to one and also used the scans to collect anatomical data including the compressing vessels and severity of neurovascular compression (NVC), further enhancing the study.

Both studies used the retrosigmoid approach when carrying out MVD. The validity of Inoue, T. *et al.* (2017) was strengthened by obtaining 3D images of the craniotomy site with contrast-enhanced CT scans to identify the exact site of the transverse-sigmoid junction. Additionally, 3D images of the trigeminal nerve and adjacent structures were created using GammaPlan® (ELEKTA, Stockholm, Sweden) to determine the anatomical relations between the nerve and vessels.

Dai, Z. *et al.* (2016) went into greater detail on the surgical procedure of MVD including incisions and type of material used for vessel-nerve separation.

For GKS:

Inoue, T. *et al.* (2017) used a median dose of 88 Gy which is within the recommended dosage where as Dai, Z. *et al.* (2016) used a dose of 59.5 Gy and <12 Gy at the brainstem which is below the recommended dose and could potentially reduce the efficacy and success of GKS. Dai, Z. *et al.* (2016) also admits that the study shows that the optimal radiation therapeutic dose range was 70–90 Gy. However, having said that, in Inoue, T. *et al.* (2017) irradiation was performed with a single isocentre whereas in Dai, Z. *et al.* (2016) it was carried out with two isocentres.

Outcomes Assessed

The 2 studies have similarities in the assessed outcomes and also differences, some of which enhance their strengths and some of which weaken them.

Both studies assess pain relief, recurrence and complications.

Both studies use the BNI pain scale to measure pain relief, however Inoue, T. *et al.* (2017) measures numbness using the BNI numbness scale and combines the two scores together to give a separate outcome score, increasing its strength. Dai, Z. *et al.* (2016) on the other hand, includes numbness with all other complications and does not give it a specific score. However, Dai, Z. *et al.* (2016) used the Visual Analog Scale (VAS) to measure pain relief in conjunction with the BNI scale which increases the reliability of the results.

Inoue, T. *et al.* (2017) assessed the outcomes at least 1-year post-surgery, however in some cases this was 1-year post-surgery and in some cases 11-years post-surgery which makes the results much more difficult to compare and weakens the evidence. Dai, Z. *et al.* (2016) on the other hand, assessed the patients regularly at fixed intervals of less than 6 months, 6-12 months and 24 months post-surgery, making the results much more comparable and strengthening the results over Inoue, T. *et al.* (2017).

Recurrence was clearly defined by Inoue, T. *et al.* (2017) as ‘any degree of recurrent pain requiring medication and/or additional surgical procedures after reaching a medication-free status’ (BNI Score 3 or higher). Dai, Z. *et al.* (2016) however, does not define recurrence which highlights a major flaw in the study.

Inoue, T. *et al.* (2017) reports severe dry eye, hearing disturbance, masticatory weakness and cerebellar dysfunction as complications where as Dai, Z. *et al.* (2016) reports corneal reflection loss, facial numbness, herpes zoster, facial paralysis and hearing loss. Due to the differences in complications reported by the two studies, it is difficult to compare and state whether one procedure is safer than the other. However, Numbness & hearing loss were common between the two studies and can be compared.

Statistical Analysis
Both studies used the χ^2 test to determine P-Values and considered $P<0.05$ to be statistically significant. Inoue, T. *et al.* (2017) used the Student’s t-test to analyse continuous data where as Dai, Z. *et al.* (2016) used the independent samples t-test.

When it came to analysing categorical data Inoue, T. *et al.* (2017) used two-tailed fisher exact tests where as Dai, Z. *et al.* (2016) used the χ^2 test and the Mann−Whitney U test. Both studies used Kaplan-Meier analysis curves to determine pain relief over time.

Dai, Z. *et al.* (2016) has an advantage over Inoue, T. *et al.* (2017) as the former used Binary logistic regression was to analyse how preoperative factors (sex, age, disease course, pain distribution, and VAS scores) influenced postoperative pain relief, where as the latter study did not.

Conclusion of Evidence
Both studies found statistically significant differences showing that MVD is more successful than GKS in treating TN and and provides superior clinical outcomes. However, both studies have several weaknesses, including some major flaws. Not only this but as MVD is a much more invasive procedure requiring many patient and health factors to be taken into account before choosing surgery type. Not only this, but there may be many other studies which use other pain indices which must also be taken into consideration. Based on the evidence and above considerations, further evidence is needed in the form of a larger and randomised control trial using only otherwise fit and healthy patients in order to categorically state which procedure is more successful in treating TN.

VI. IMPLICATIONS FOR FUTURE PRACTICE & RESEARCH

Clinical Practice
MVD and GKS are amongst the most widely used procedures to surgically treat Trigeminal Neuralgia. Whilst no guidelines exist to recommend one surgery over the other, MVD and GKS both have their strengths and weaknesses. MVD is an invasive procedure, however it is the only procedure that does not involve damaging the trigeminal nerve. On the other hand, GKS in the only non-invasive procedure, however it involves damaging the trigeminal nerve. The evidence shows that MVD gives superior outcomes than GKS, however MVD is invasive and may not be the preferred choice in elderly and more medically compromised patients. Whilst they have many strengths, both studies in question are subject to several weaknesses, bias and flaws.

Based on this, if a patient comes into dental practice seeking advice on this matter, I cannot advise explicitly suggesting one surgery over the other to the patient. Having said that, the GDP may let their patient know that the evidence does seem to suggest MVD results in superior outcomes to GKS however, the GDP must also inform the patient that many factors, both patient, operator and procedural need to be taken into account and advice & examination under a specialist must be sought before any decision is made.

Research

Further investigation is required and a study should be designed to disprove the following null hypothesis:

'Microvascular Decompression is less effective than Gamma Knife surgery for the surgical Management of Trigeminal Neuralgia'

The study should improve on Inoue, T. *et al*. (2017) and Dai, Z. *et al*. (2016) in the following ways:

Patient Grouping
Both Inoue, T. *et al.* (2017) and Dai, Z. *et al.* (2016) used a small number of patients (231 & 202 respectively) and patients were from a single centre. The new proposed study should determine a sample size using a power value of 90%, with an equal number receiving both treatments and the study should be multi-centred. Not only this but the male:female ratio should also be balanced with patient ethnicity being recorded, which neither of the 2 studies implemented.

The study should also include patients who are generally fit and healthy and from within a narrower age range so as to reduce patient factors affecting the success of either surgery and thus invalidating and weakening the results. This also allows patients to be randomly allocated an intervention as they should be able to undergo either procedure.

Both studies only used patients with Classical TN and this should be replicated for this design.

Intervention Details
Neither of the two studies mentioned how many operators carried out the MRI/MRTA scans. Pre-operative MRI scans should be carried out by a single operator/assessor to exclude the presence of intracranial lesions, including neoplasms, and to confirm the neurovascular relationships.

Neither of the 2 studies mentions how many surgeons carried out the procedures which may lead to bias and reduced accuracy of the results. MVD should be carried out by a single surgeon with expertise and significant experience in carrying it out. Likewise, GKS should be carried out by another surgeon with expertise and significant experience in carrying it out. This reduces bias and also helps to increase consistency in executing successful surgeries.

Dai, Z. *et al.* (2016) concluded that the optimal radiation dose for GKS should be 70-90 Gy and this is consistent with current literature. Inoue, T. *et al.* (2017) used a median dose of 88 Gy which is also within the recommended dosage, therefore, in this study GKS should be carried out at a fixed dose between 70-90 Gy.

Outcomes Assessed
A weakness within Inoue, T. *et al.* (2017) is that follow-up was conducted anytime, 1 year after surgery, meaning that some patients were followed-up several years after their surgery and others as little as 1 year after surgery. This is a major flaw on Inoue, T. *et al.* (2017)'s part that Dai, Z. *et al.* (2016) avoided by following up with patients at regular fixed intervals, and this should be replicated.

In this study, patients should be assessed and followed up at regular intervals of 6 months, 12 months, 24 months and 48 months post-surgery. This will increase the strength of the study and gives a much more accurate representation of the long term outcomes of the two procedures.

Dai, Z. *et al.* (2016) not only used the BNI scale but also the VAS scale which increases the validity of the results over Inoue, T. *et al.* (2017) who only used the BNI scale. Based on the fact that the BNI scale was specifically made for Trigeminal Neuralgia and the VAS is amongst the most widely used pain scales, both of these should be used in this study. Inoue, T. *et al.* (2017) used the BNI numbness scale also and used both BNI scores to come up with an overall score and this should be replicated for this study.

Recurrence should be defined and recorded as BNI score 3 or higher as Inoue, T. *et al.* (2017) did. Complications should also be recorded as in both studies, with numbness being recorded separately using the BNI Numbness score.

Key Results
The Chi Squared test and Student's T-test from Inoue, T. *et al.* (2017) should be repeated with statistical significance assumed at $P<0.05$ as both studies did. Neither study used Power intervals which should be included in this study as well as 95% confidence intervals which only Dai, Z. *et al.* (2016) used. Both studies used Kaplan-Meier analysis curves to determine pain relief over time and should be repeated for this particular study.

VII. RESEARCH PROTOCOL

Title	Comparing the effectiveness of Microvascular Decompression and Gamma Knife Surgery for the Surgical management of Trigeminal Neuralgia.
Aim	To determine whether Microvascular Decompression is more effective in treating Trigeminal Neuralgia than Gamma Knife Surgery.
Null Hypothesis	Microvascular Decompression is less effective than Gamma Knife Surgery in treating Trigeminal Neuralgia.
Study Design	Study Type A single blind, multicentre, randomised controlled trial Inclusion Criteria • Patients with Classical Trigeminal Neuralgia • No prior surgery for Trigeminal Neuralgia • Age 18-50 • No significant illness, disease or condition making patients unable to undergo either surgery Exclusion Criteria • Patients with any intercranial lesions or tumours • Patients with Painful Trigeminal Neuropathy (previously known as Symptomatic/Secondary TN)
Patient Grouping	An independent statistician will be used to calculate a suitable sample size using a power calculation with a power of 90% at a statistically significant P-value of 0.05. Participants in the study will be selected from Outpatient centres throughout the UK, with equal numbers of each gender, irrespective of race and socio-economic background. This will ensure the external validity of the study. In order to compensate for drop-outs, an additional 15% of patients will be recruited. Patients will be randomly allocated to either MVD or GKS using computer-generated randomisation. The study will be single blind as the post-surgery outcomes assessor will be unaware as to which surgery patients have undergone.
Intervention Details	Whilst it may be very time consuming, to reduce bias, a single surgeon with the relevant experience and expertise in MVD will carry it out, likewise another single surgeon with the relevant experience and expertise in GKS will carry it out. Both surgeons will not be blinded due to the obvious nature of the procedures. Both surgeons should be well trained and up to date to a standardised level of teaching. Instrumentation and equipment will be provided by an independent supplier to ensure standardisation and prevent bias. Pre-operative MRI scans will be carried out by an independent evaluated radiographer and reported by an independent evaluated radiologist. MVD will be carried out using the same standardised material to separate vessel and nerve for each patient. GKS will be carried out using a single isocentre at a dose of 70-90 Gy.
Outcomes Assessed	Primary Outcomes: 1. Pain Relief 2. Pain Recurrence Secondary Outcome: 1. Complications Outcomes will be assessed by an independent body 12 months, 2 years and 4 years after surgery. Pain relief will be measured using both the BNI and VAS pain scales. The BNI Numbness scale will be used to measure numbness after which both BNI scores will be added to give an overall score. Recurrence will be recorded and will be defined as BNI score 3 or higher. Any complications that occur during the surgeries will be recorded. Binary logistic regression will be performed to analyse how preoperative factors influence postoperative pain relief with 95% confidence intervals.
Key Results	The Chi Squared test and Student's T-test will be carried out with statistical significance assumed at $P<0.05$. Kaplan-Meier analysis curves will be used to determine pain relief over time.
Time Frame	The study will be conducted over a 4-year period

Resource Requirements & Budget	An independent source with no input in the study should provide the necessary resources and funding
Expected Outcome	This study will help to determine whether MVD is more effective than GKS in the surgical management of Trigeminal Neuralgia
Dissemination of Results	The evidence presented by the study will be reported in peer reviewed publications and appraised. Depending on these results, the intervention can be implemented as necessary

Table 5: Research protocol for suggested future randomised control trial

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