Stimulation of the Gasserian Ganglion for Trigeminal Neuropathic Pain Refractory to Medical Management

Jessica Smedley

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Abstract

Background: Trigeminal neuropathic pain (TNP) is an often debilitating facial pain syndrome for which there is no known cure or effective treatment. It differs from its more commonly known counterpart, trigeminal neuralgia (TN), in that it is constant and does not have an anatomical etiology which would allow for surgical correction. TNP is frequently refractory to pharmacologic therapy using high dose antiepileptics. Previous attempts to use nerve stimulation as a treatment method involved invasive surgical techniques and frequent electrode migration.

Methods: Exhaustive search of available medical literature was conducted using Clinical Key, MEDLINE-Ovid and Web of Science and the following search terms: trigeminal neuropathic pain, neuromodulation and stimulation. Articles were assessed for quality using GRADE criteria.

Results: Two case series studies fit all eligibility criteria. Each utilized a temporary electrode placed for a trial period to assess efficacy and determine candidacy for permanent implantation. One study found that in those with a positive trial, 96.3% at 6 months and 46.7% of patients at 24 months experienced pain reduction from baseline. Another study found that 62.5% of patients with a positive trial experienced pain reduction at 6 months, with 37.5% still experiencing pain reduction at 12 months.

Conclusion: Stimulation of the Gasserian ganglion (GG) may be an effective treatment for long-term pain reduction in TNP; however, current studies are of very low quality due to small cohort size and lack of an RCT.

Keywords: Trigeminal neuropathic pain, Gasserian ganglion, trigeminal neuropathy, stimulation, neuromodulation

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Jessica Smedley

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Heather Porst, MMSc, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Jessica Smedley is an Oregonian and a proud alumnus of Washington State University where she majored in Biology. Prior to PA school she enjoyed a career as a respiratory therapist working primarily at the VA where she established the VA’s first telemedicine program for sleep disordered breathing. She is married to her college sweetheart, Doug, and loves to spend her spare time exploring the Pacific Northwest.
Abstract

**Background:** Trigeminal neuropathic pain (TNP) is an often debilitating facial pain syndrome for which there is no known cure or effective treatment. It differs from its more commonly known counterpart, trigeminal neuralgia (TN), in that it is constant and does not have an anatomical etiology which would allow for surgical correction. TNP is frequently refractory to pharmacologic therapy using high dose antiepileptics. Previous attempts to use nerve stimulation as a treatment method involved invasive surgical techniques and frequent electrode migration.

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Acknowledgements

To my mom, who is courageously living with trigeminal neuropathic pain and inspires everyone around her to live generous and faithful lives. I will never stop searching for ways to help you.
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List of Abbreviations
GG  Gasserian ganglion
RCT randomized control trial
TN  trigeminal neuralgia
TNP trigeminal neuropathic pain
VAS  visual analogue scale
Trigeminal Nerve Stimulation for Trigeminal Neuropathic Pain Refractory to Medical Management

BACKGROUND

Trigeminal neuropathic pain (TNP) is a chronic, often debilitating, facial pain syndrome for which there is no adequate treatment. It’s quality and severity vary amongst patients, as does its etiology—most commonly direct injury to the trigeminal nerve leading to neural damage via trauma, dental procedures, or zoster infections. TNP can also be idiopathic.¹ TNP can affect any combination of the three branches of the fifth cranial nerve. TNP, and its more popular counterpart, trigeminal neuralgia (TN), are believed to be “one of the most severe pain types known to humanity,” and were previously referred to as ‘suicide disease’ given the large burden of people who took their own lives as a result of their intractable pain.²

Both TNP and TN share similar etiologies but differ in their diagnostic criteria and treatment approach. Although TN can be subclassified by etiology, “classic” TN requires that an anatomical cause—such as neurovascular compression or a plaque (ie multiple sclerosis) is seen on MRI.¹,³ The presence of this anatomical relationship allows for targeted treatment--microvascular
decompression of the affected area. Additionally, classic TN is characterized by brief, paroxysmal ‘attacks’ of shock-like pain with periods of complete relief between episodes and is primarily unilateral. People with TNP, however, experience a continuous background pain often described as pins and needles or as burning pain, but also experience overlying attacks in addition to the smoldering pain they experience at baseline. They may also not have any evidence of neurovascular compression on imaging and more commonly experience bilateral symptoms. Sensory deficits are also more likely to accompany TNP than TN.¹

Currently, the standard of care for TNP is treatment with high dose antiepileptics (primarily carbamazepine and oxcarbazepine), tricyclic antidepressants (TCAs), and opiates.⁴ Long term high doses of these medications carry a heavy side effect profile including dizziness, drowsiness and GI upset.⁵ A prior study investigated neurovascular decompression as a non-pharmacologic treatment for TNP, as it is in classic TN, but found that not only was this ineffective, it worsened pain in 73% of patients.⁶

Targeted therapies of the trigeminal nerve, namely within the Gasserian ganglion (GG), have been a topic of interest in the treatment of TNP since the 1970s. The GG, also known as the trigeminal ganglion and less often, the semilunar ganglion, lies
between where the trigeminal nerve exits the pons and where it splits into its 3 primary branches. In the 1984, Meglio developed a percutaneous approach to GG stimulation which resulted in pain relief in 86% of participants, however electrode dislocation and refining the surgical approach were still issues. Although technology and techniques have improved vastly since this time, there has been little published research focusing on just those with TNP, not TN, in recent years and the standard of care remains pharmacologic treatment.

This literature review aims to determine if recent research supports stimulation of the GG for refractory trigeminal neuropathic pain as an effective treatment to reduce pain.

**METHODS**

An exhaustive search of literature was performed using Clinical Key, MEDLINE-Ovid, and Web of Science. Keywords used included: trigeminal neuropathic pain, stimulation, and neuromodulation. Studies were required to include only patients with TNP who were refractory to standard pharmacologic treatment. Studies that included patients with diagnoses of TN were excluded. Additional inclusion criteria included: studies in the English language, human studies, and
studies published within the last 15 years. Articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).  

**RESULTS**

The literature search yielded 182 articles for review. After removing duplicates and screening for relevant articles using exclusion criteria, there were 2 qualifying studies remaining\(^ {10,8}\), both of which were case studies (Figure 1). Both studies were deemed to be very low quality given the inherent nature of case studies (Table 1). Currently no randomized controlled trials exist on this specific topic. Both studies\(^ {10,8}\) utilized the visual analogue scale (VAS) to evaluate pain severity pre and post intervention.

**Kustermans et. al**

This study\(^ {10}\) was a 24-month retrospective analysis of 22 patients with TNP refractory to medication management. All underwent trigeminal nerve stimulation at the level of the GG between 2010-2015 at a single center in Belgium. Etiologies of TNP varied; however, in 82% of patients (18/22), the etiology was iatrogenic secondary to a surgical intervention. Patient ages ranged from 32-76 with a mean age of 59. Sixteen patients were female. The mean VAS pain score prior to intervention was 9/10 (range 6-10).\(^ {10}\)
The authors conducted a 4-week trial of stimulation using a customized electrode and proceeded to permanent implantation for anyone who experienced subjective pain reduction during the trial. Seventeen (77.3%) patients met criteria based on subjective pain reduction (15 of whom experienced >50% reduction in pain) and received permanent implantation of the electrode. One of the original 22 patients could not be evaluated for permanent implantation secondary to requesting and receiving euthanasia.\textsuperscript{10}

At 6 months, an additional patient failed to reach follow up secondary to suicide. Fifteen of the remaining 16 (93.8%) continued to experience pain reduction.\textsuperscript{10}

At 24 months, another patient failed to reach follow up secondary to suicide. Seven of the remaining 15 (46.7%) of patients continued to experience pain reduction. Two had completely ceased use of any pain medication. The authors found a positive predictive value of 44% for long-term pain relief following a positive trial period.\textsuperscript{10}

Several complications were noted in the 17 patients that underwent permanent implantation. Seven patients (41%) experienced some level of physical discomfort such as muscle cramping or neck fibrosis where the electrode met the lead. The authors propose that a longer electrode would allow for a more
advantageous surgical technique and reduce the incidence of this complication. Additionally, four patients (24%) experienced an intra-oral erosion secondary to implantation.\textsuperscript{10}

\textbf{Machado et. al}

This study\textsuperscript{8} included 10 patients (5 male, 5 female) with TNP that had exhausted pharmacologic management. The etiology of TNP in this population was dental, traumatic, or surgical in nature and involved various combinations of involvement in all 3 branches of the fifth cranial nerve. Median age of patients was 46 years (range 37-65). Visual analogue scale (VAS) pain questionnaires (0-10) were completed at baseline and again post-implantation at 1 month, 6 months, and 1 year.\textsuperscript{8}

An initial 7-10 day trial period of trigeminal nerve stimulation at the level of the GG was conducted using an external electrode (Medtronic). All patients were implanted using a similar surgical technique. Machado et. al defined a successful initial trial of 7-10 days as >50% pain reduction on the VAS pain scale. At the end of this trial, 8 patients met criteria for a successful trial and went forward with permanent implantation. The baseline mean VAS score in the 8 patients that proceeded to permanent implantation was 6.5/10. The mean VAS was not reported for the initial 10 included in the trial.\textsuperscript{8}
At 6 months, 3 of the 8 patients were withdrawn from the study due to explantation secondary to loss of efficacy (2) and no follow-up (1). Of the 5 patients remaining, 3 still continued to experience >50% pain reduction (mean VAS score 3/10, range 3-3) at 12 months and 2 no longer had significant change in pain score compared to baseline (mean VAS 7/10, range 7-7). Of the 3 that experienced continued pain relief, 2 were able to reduce opioid intake by 50% and 1 was able to completely cease opioid use. There were no post-procedural complications to report in this study.  

DISCUSSION

TNP can be a debilitating facial pain condition and frequently does not respond to the traditional treatment of high-dose epileptics. Surgical intervention is not widely used due to a lack of quality research. Pharmacologic options are quickly exhausted and carry a large profile of side effects at the doses needed to lessen pain to a manageable level.

Given the nature of case studies, the quality of this research is poor. However, there does seem to be some promise in the little data available. Both studies\textsuperscript{10,8} demonstrated success in long-term pain reduction at 12-24 months at 46.7% and 30%, respectively. However, an even greater number experienced at least short-term pain relief at 6 months: 93.8% and 62.5%, respectively. In the largest of these
studies\textsuperscript{10}, 80% those that experienced a lack of efficacy in the electrode after initial success did so after six to 24 months. It is unclear what the patient perspective is on the risks versus benefits on even short term relief.

Each study included patients with varying combinations of branch involvement resulting from multiple etiologies (traumatic, dental, post herpetic). Patients were from similar age groups with mean ages of 59 and 56, respectively, and all had previously attempted to achieve pain relief through pharmacologic management.

Each study required an initial trial, used a similar surgical technique for implantation aimed at the GG, and followed patients for a minimum of 1 year to measure pain reduction. Initial trial lengths to determine candidacy for long term implantation varied (1 week\textsuperscript{8} versus 4 weeks\textsuperscript{10}); however, both allowed for patient control of the frequency generator in the initial trial phase to determine an effective level for pain control. It is not reported in the study with a 4-week trial\textsuperscript{10} if the frequency selected by the patient was any different at the end of the first week and the end of the fourth week, and this could be valuable knowledge to help determine an appropriate future trial length.

Some variance existed amongst trials regarding the qualifying criteria to move a patient forward from a trial to a permanent implant. Machado et al study\textsuperscript{8} defined a successful trial as >50% reduction in
pain whereas Kustermans et al\textsuperscript{10} counted success as any subjective relief in pain. However, in the Kustermans et al study,\textsuperscript{10} 88\% of patients experienced >50\% pain reduction in the initial trial. Unfortunately, Kustermans et al\textsuperscript{10} did not provide data on if those that experienced less than 50\% pain relief initially were a part of the group that eventually experienced long-term pain relief. At this time, it is unclear whether >50\% pain reduction is a predictor for long-term success. Moreover, each study utilized a different electrode which could account for variances in success rates.

Kustermans et al\textsuperscript{10} was the largest of the 2 studies with 22 enrolled however this is still considered a small sample size. Moreover, 16 of these patients were female, making this demographic unbalanced. Perhaps the greatest flaw in this trial is that the 3 patients (13.6\%) that ended their lives during the trial were not accounted for in the calculation of trial success rates. It is unclear if suicide, and in 1 case euthanasia, were related to an unsuccessful trial due to inadequate pain relief or related to other issues. This information would be critical to include in these calculations. Instead, they were reported as “lost to follow up” and removed from success rate calculations.\textsuperscript{10}

Another concern of the Kustermans et al trial\textsuperscript{10} is the use of a custom made lead which can make reproducibility an issue for future
trials. This lead was made in partnership with a larger manufacturer, Medtronic, but it is unclear if it would be available for future research. The authors did hypothesize that a longer electrode would reduce the complications experienced in the trial, but this has not been investigated.¹⁰

The loss of 3 patients to either suicide or euthanasia in the Kustermans et al trial¹⁰ cannot be overemphasized as it speaks to the burden of this condition. In this trial¹⁰, nearly 2/3 of patients had a history of or currently met criteria for a major mood or anxiety disorder. Although there are currently no estimates on the number of people who take their lives secondary to poorly managed TNP, the cyclical relationship between chronic pain and depression has been well established.³ Psychological evaluation should be a critical part of assessing and treating these patients.

The Machado et al study⁸ was limited by extremely small sample size and technical complications. However, the subject population was homogenous and follow-up was adequate. The authors hypothesize that electrode migration could have affected outcomes for long-term efficacy and that their anchoring technique could be improved.⁸

There is a clear lack of quality research on trigeminal nerve stimulation for refractory TNP. Of the studies that do exist, most include patients with TN and do not exclusively look at those with TNP.
Currently no RCTs exist, but the plausibility of conducting a study like this is uncertain. Without larger and higher quality research on this intervention, it is less likely to be considered as a treatment option. Additionally, further research could help to identify ideal candidates and trial length as well as to evaluate safety.

CONCLUSION

GG stimulation for TNP is minimally invasive and has not been shown to have significant morbidity nor any mortality associated with this intervention. However, no specific safety studies exist and should be explored alongside lead design and implantation techniques.

Although the majority of patients in these studies did not experience long term pain relief, given the high level of suffering with this condition it could be considered as a treatment option when pharmacologic management has failed. Moreover, this intervention could be considered early in treatment given the psychological impact of chronic pain. Expectation management with the patient is crucial. Neither study evaluated whether patients that experienced even short term pain relief, or those that experienced a complication, still found the intervention beneficial.
References


Figures

Figure 1.

**PRISMA 2009 Flow Diagram**

1. **Identification**
   - Records identified through database searching (n = 182)
   - Additional records identified through other sources (n = 0)

2. **Records after duplicates removed (n = 144)**

3. **Screening**
   - Records screened (n = 10)
   - Records excluded (n = 3)

4. **Eligibility**
   - Full-text articles assessed for eligibility (n = 7)
   - Full-text articles excluded, with reasons (n = 4)

5. **Included**
   - Studies included in qualitative synthesis (n = 2)
   - Studies included in quantitative synthesis (meta-analysis) (n = 2)
## Tables

### Table 1: Quality Assessment of Reviewed Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kustermans et al(^{10})</td>
<td>Case series, retrospective</td>
<td>Very Serious(^{a})</td>
<td>Serious(^{b})</td>
<td>Not serious</td>
<td>Very Serious(^{c,d})</td>
<td>Not likely</td>
<td>None</td>
<td>Very Low</td>
</tr>
<tr>
<td>Machado et al(^{8})</td>
<td>Case series, prospective</td>
<td>Very Serious(^{a})</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^{c})</td>
<td>Not likely</td>
<td>None</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

\(^a\) No control group  
\(^b\) 16/22 patients were female  
\(^c\) Small sample size  
\(^d\) High attrition rate