The Value of Cryosurgery in the Management of Trigeminal Neuralgia: a Systematic Review

M. Lindström
N. Thuring

Handledare: S.Isaksson, M.Rohlin

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The Value of Cryosurgery in the Management of Trigeminal Neuralgia: a Systematic Review
M. Lindström¹*, N. Thuring²*, S. Isaksson³§, M. Rohlin⁴

¹Dental student, Faculty of Odontology, Malmö University, Malmö, Sweden
²Dental student, Faculty of Odontology, Malmö University, Malmö, Sweden
³Department of Oral and Maxillofacial Surgery, Halland hospital, Halmstad, Sweden
⁴Department of Oral Radiology, Malmö University, Malmö, Sweden

*These authors contributed equally to this work
§Corresponding author

Email addresses:
ML: otl07030@student.mah.se
NT: otl07019@student.mah.se
SI: Sten.G.Isaksson@regionhalland.se
MR: madeleine.rohlin@mah.se

Key words
Trigeminal Neuralgia, Cryosurgery, Cryotherapy, Freezing, Treatment Outcome, Adverse Effects, Systematic Review

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Abstract
The aim of this study was to evaluate the evidence for pain relief and adverse effects following cryosurgery in the treatment of patients with trigeminal neuralgia through a systematic review. A praxis investigation was carried out in order to establish how common this treatment is among 44 Oral and Maxillofacial clinics in Sweden. The systematic review was conducted according to Goodman’s systematic approach. The search for literature was conducted in Medline, The Web of Science and the Cochrane Database. Out of 45 retrieved studies, six met the pre-determined inclusion criteria. The reported duration of pain relief following cryosurgery varied in a wide range (from zero days to four years). No conclusions regarding the pain relief could be drawn from the included studies. The reported adverse effects following cryosurgery was minor and consisted of temporary sensory loss, migration of pain to another division of the trigeminal nerve and small oedema. Five clinics that currently use a cryosurgical treatment in the management of trigeminal neuralgia were identified.

Introduction
Trigeminal neuralgia is defined by the National Institute of Neurological Disorders and Stroke (NINDS) as “a chronic pain condition that causes extreme, sporadic, sudden burning or shock-like face pain.” The pain occurs in paroxysms, with each interval ranging from a few seconds to two minutes and the pain can be both physically and mentally incapacitating (1). Even suicides associated with the diagnosis have been reported (2). The pain may be triggered spontaneously or by stimulation of certain trigger points and is typically felt on one side of the jaw or cheek. Daily activities such as eating, tooth brushing and talking may stimulate these trigger points and release pain outbursts (1, 3).
Trigeminal neuralgia is a relatively rare condition with a prevalence around 4-6 per 100,000 people in 1990’s in the US (9). More recent studies in the UK suggest that trigeminal neuralgia is more common with a prevalence of 29 per 100,000 people (10). Age is a primary risk factor and symptom manifestation is more likely to occur after the age of 50 years (1, 11).

There are different theories about the mechanism causing the pain in trigeminal neuralgia. Dever et al 2002, described that the trigeminal nerve, at the root entry zone (where the trigeminal nerve enters the pons), is very sensitive to compression from the surrounding tissue (Figure 1). Vessels that pass through this zone might lead to demyelination and result in an abnormal firing of impulses (4).

Multiple Sclerosis is seen in 2-4% of the patients with trigeminal neuralgia, where a demyelination also is present (5). A recent study described a high ratio of A/C-fibers in the superior part of the nerve in the root entry zone. A compression of the superior area which has been observed in more than 50% of the compression injuries caused by vessels could explain the characteristics of the pain associated with trigeminal neuralgia (6, 7). Other aetiologic factors might be neoplasms, trauma or viral infections (8).

The first line of treatment of trigeminal neuralgia is often comprised by medication of antiepileptic drugs. When medical treatment fails i.e lack of pain relief or exaggerated adverse effects, surgical treatment might be considered as the next available treatment option (12). Surgical methods may also be considered when patients are heavily medicated due to the risk of polypharmacy (13).
Surgery can be performed peripherally on nerves or centrally in the posterior fossa of the skull. Peripheral surgical techniques are less invasive than central ones and do not require a medically fit patient (14).

The central procedures involves separation of the trigeminal ganglion from surrounding compressing arteries, veins or tumors (micro vascular decompression (15)), electrical induced heating of the ganglion (percutaneous radiofrequency thermocoagulation (16)), compression of the ganglion (percutaneous ballon compression (17)) or radiation of the ganglion (gamma-knife radiosurgery (18)).

The peripheral procedures involves injection of alcohol, glycerol or local anesthetic agents in the peripheral branches of the trigeminal nerve. Excision of the peripheral branch (peripheral neurectomy) or freezing (cryosurgery) may be optional treatments (13). In cryosurgery, a cryoprobe with either nitrous oxide or liquid nitrogen, as a refrigerant, is applied peripheral to the isolated nerve (Figure 2).

Cryosurgery as a treatment for trigeminal neuralgia, first described by Lloyd et al. 1976 (19), has not been extensively evaluated. It is not clear how efficient it is as a pain relieving method, nor what side effects are associated with the treatment (20).

The aim of this study was to evaluate evidence for the outcomes of cryosurgery as a pain relieving method in the treatment of trigeminal neuralgia. Furthermore, the praxis of this method in Oral and Maxillofacial Surgery clinics in Sweden will be studied.
Methods and Material
The systematic review was conducted according to Goodman’s systematic approach (21) and comprised the following steps (1) problem specification, (2) formulation of a plan for the literature search, (3) literature search and retrieval of publications, and (4) data extraction, interpretation of data and evaluation of evidence from literature retrieved.

(1) Problem specification:
- What evidence is available for the treatment of trigeminal neuralgia with cryosurgery as a pain relieving method?
- If initial successful, what is the duration of pain relief?
- What risks and adverse effects are associated with this treatment?
- How many Oral and Maxillofacial surgery clinics in Sweden implement cryosurgery in the management of trigeminal neuralgia?

Formal definitions for the following elements were sought prior to the literature search by means of Medical Subject Heading terms (MeSH) in Medline:

- Trigeminal Neuralgia: A syndrome characterized by recurrent episodes of excruciating pain lasting several seconds or longer in the sensory distribution of the trigeminal nerve. Pain may be initiated by stimulation of trigger points on the face, lips, or gums or by movement of facial muscles or chewing. Associated conditions include Multiple Sclerosis, vascular anomalies, aneurysms, and neoplasms.

- Cryosurgery: The use of freezing as a special surgical technique to destroy or excise tissue.
- Cryotherapy: A form of therapy consisting in the local or general use of cold. The selective destruction of tissue by extreme cold or freezing is cryosurgery.

- Treatment outcome: Evaluation undertaken to assess the results or consequences of management and procedures used in combating disease in order to determine the efficacy, effectiveness, safety, practicability, etc., of these interventions in individual cases or series.

- Adverse effects: Used with drugs, chemicals, or biological agents in accepted dosage or with physical agents or manufactured products in normal usage - when intended for diagnostic, therapeutic, prophylactic, or anesthetic purposes. It is used also for adverse effects or complications of diagnostic, therapeutic, prophylactic, anesthetic, surgical, or other procedures, but excludes contraindications for which "contraindications" is used.

Definitions of elements, not according to MeSH terms:

- Freezing: Liquids transforming into solids by the removal of heat.

- Cryoanalgesia: The relief of pain by application of cold by cryoprobe to peripheral nerves.

(2) Formulation of a plan for the literature search
Literature search was conducted in three databases, Medline, the Cochrane Library and the Web of Science. The search in Medline is presented in Table 1 and the search in Web of Science in Table 2. The searches were conducted in November 2011 with the help from a librarian at the Malmö University. A search through the reference lists of included studies was also made to find additional publications. The searches were
limited to studies on humans and to those written in the English, Swedish, Danish or Norwegian language.

(3) Literature search and retrieval of publications
Studies found were identified and processed with application of inclusion and exclusion criteria. The inclusion and exclusion criteria are presented in Table 3. Patients had to be diagnosed with trigeminal neuralgia. Prior to treatment, a diagnostic blockade had to be administered to verify the affected nerve branch. To be able to assess the pain relieving ability of the cryosurgical method, the surgical procedures exclusively had to be cryosurgical. Cryosurgical techniques other than those administered peripherally were also excluded. It was fundamental that a post treatment evaluation (minimum three months) was conducted – in order to estimate the length of patient’s pain free periods.

(4) Data extraction, interpretation of data, and evaluation of evidence from literature retrieved
To assess the quality of included publications, each study was read and scored, by both authors, independently using a protocol based on the STROBE-statements used to assess observational studies (22). The STROBE-protocol included 22 criteria to evaluate the methodological quality of each study. Each criterion was given equal weight and considered to be met or not met. Evidence was rated according to GRADE guidelines in one of four quality levels – high, moderate, low or very low (23). When there is no study of moderate quality evidence will be assessed as insufficient.

Investigation of praxis
In order to establish the praxis of cryosurgical technique amongst Oral and Maxillofacial Surgeons in Sweden, a questionnaire was sent to the 44 Oral and
Maxillofacial Surgery clinics registered as members of the Swedish Association of Oral and Maxillofacial Surgeons.

Each clinic was asked two questions:

- Are patients with diagnosed trigeminal neuralgia treated in your clinic?
- If yes, are these patients treated with cryosurgery?

The questionnaire was sent via mail. Clinics which did not answer via mail were contacted by phone.

Results

Literature identification
The number of publications retrieved, read, and interpreted are presented in Figure 3.

The Medline search yielded 32 studies and the Web of Science yielded 24 studies. The Cochrane Library search yielded 4 systematic reviews, out of which one met the problem specification. As 17 publications of the Web of Science search was duplicates of the Medline search, totally 43 original studies were found. Two publications were also found searching the reference lists of included publications.

Six studies were found relevant for inclusion (Figure 3). Thirty-nine studies were excluded. Four were excluded due to language restrictions, 15 not being clinical studies, 11 not meeting the problem specification, 4 case reports, 4 due to prior treatment with alcohol injections or surgery and 1 study with inclusion of MS patients.

Interpretation of data
The results are presented in Table 4.

The duration of pain relief in patients receiving cryosurgery ranged from 0 days (19) to 4 years (24). Median duration of pain relief could not be assessed in 3 (24-26) of the 6 studies. The remaining 3 studies reported a median pain relief of 21 days (19)
235 days (27) and 18 months (28). The other 3 studies (24-26) presented the number of patient’s pain free in annual intervals. The reported frequency of patients with pain relief after one year varied between 32% (26) and 50% (24). The number of patients free of pain after two years was reported as 14.5% (25) but reported by the same research group as 18% after four years in another study (24).

The reported adverse effects were temporary sensory loss (24-28), migration of pain to another division of the trigeminal nerve (24, 25), post-operative infection (25) and small oedema (26, 28). The most commonly reported adverse effect was temporary sensory loss, which was reported in five out of six studies. Sensory loss ranged between two to four months. None of the studies presented any case of permanent sensory loss or anesthesia dolorosa.

**Evaluation of evidence**
The study quality of the included studies was low therefore evidence is insufficient to determine the pain relieving effect of cryosurgery in patients with trigeminal neuralgia. There is low evidence that the most frequent adverse effect following cryosurgical treatment of trigeminal neuralgia patients is sensory loss.

**Investigation of praxis**
Forty-four clinics answered the questionnaire i.e. 100%. The answers regarding treatment of trigeminal neuralgia were diverse and insufficient to analyze. Five clinics reported that they currently use cryosurgery in the management of trigeminal neuralgia.
Discussion

Methodological considerations
The search limitations regarding language restrictions may have resulted in that a few relevant publications were excluded. This may have resulted in loss off valuable data for this review. The studies included in this review were both prospective and retrospective. No study was designed as a randomized controlled trial (RCT). The quality of studies concerning cryosurgery in trigeminal neuralgia could be questioned as RCT studies would have been preferable to strengthen the scientific value. However due to patients’ severe pain associated with the disease, RCT studies might be unethical. The STROBE protocol (22) was used to evaluate the quality of the included studies. All studies were scored low, indicating the need for well structured and higher quality studies.

Discussion of results
Diagnosis of trigeminal neuralgia relies almost entirely on the basis of clinical diagnostic criteria, except for some cases where imaging studies can identify lesions along the trigeminal sensory pathway (7).

The usage of strict diagnostic criteria is crucial to ensure a correct trigeminal neuralgia diagnosis, since the diagnosis of primary (idiopathic) and secondary (i.e. tumours or multiple sclerosis) trigeminal neuralgia may have different success rates (29). The included studies in this review mainly originated from the eighties where the research methodology was not as developed as it is today. These studies lack a consistency in the reported diagnostic criteria being used.
The assessment of pain relief was deficient and the studies did not use any systematic measurements of pain, pre- or postoperatively. Since none of the studies presented a baseline of experienced pain relief it is difficult to draw any conclusions. The assessment of patient’s quality of life is more frequently used in contemporary research, and is of great importance when evaluating the success of a method. None of the included studies evaluating cryosurgery for trigeminal neuralgia did measure patient’s quality of life following treatment. Patients were considered either relieved of pain or not, but the studies did not take into consideration that a partial relief may have a great improvement in a patient’s quality of life. At least two studies included in this review (26, 30) have reported of patients being able to reduce their dosage of antiepileptic drugs following cryosurgery.

The treatment with antiepileptic drugs is associated with adverse effects such as drowsiness, dizziness, vomiting, constipation, ataxia and leucopenia (9, 20). A reduction of the dosage could offer a great improvement in patient’s quality of life because of these adverse effects. Zakrzewska and Thomas 1993 reported that 74% of patients who underwent cryosurgery treatment were willing to undergo a repeated treatment (30).

The included studies reported pain relief using different assessment. Lloyd 1976 (19) , Bernard 1980 (27) and Goss 1984 (28) presented days of pain relief in median and range, contrary to Zakrzewska 1986,1987 (24, 25) and Pradel 2002 (26) who presented the percentage of pain relieved patients in intervals of one year. The results of the studies could not be compared for pain relief as the studies used different freeze-thaw cycles and temperatures during the cryosurgery. A larger number of patients would have been advantageous regarding conclusions about pain relief, since most studies had fewer than twenty patients (19, 26-28).
Other surgical techniques have shown greater success in pain relief, e.g. microvascular decompression (MVD), where relief of pain (without medication) in 71% of the patients has been reported over a period of 10 years (15). Despite the higher success rate, MVD is a more invasive method with a risk of severe adverse effects such as hearing loss, meningitis, infarcts or haematomas (30, 31) and could be contradictive when treating patients who are heavily medicated and weak. In these patients, the minimal invasive method of cryosurgery can be a complement to the medical treatment.

Five studies out of six (24-28) reported sensory loss with a range of two to four months. All patients regained normal sensory function; no permanent sensory loss was reported. A sensory loss must be considered as an acceptable complication in relation to the severity of the pain. Occurrence of small oedema (26) following surgery and a post op infection in one patient (25) was also reported. An important finding was the occurrence of pain migration reported by Zakrzewska et al (24, 25). They presented pain migration in as much as nineteen out of thirty-nine patients, who following surgery experienced pain in an untreated nerve in the same division or in an ipsilateral, untreated division. The occurrence of pain migration might implicate a contraindication when performing cryosurgery, however, only two studies (24, 25) produced by the same authors reported this phenomenon.
**Recommendations for the future**
At least five Swedish Oral and Maxillofacial Surgery clinics are currently using cryosurgery as a treatment for trigeminal neuralgia. This advocates the need for further research concerning treatment indications and the evaluation of pain relief. Application of strict diagnostic criteria in prospective studies with a sufficient number of patients will contribute to a greater understanding concerning the pain relieving ability of cryosurgery. The collection and presentation of data must be carried out in a standardized manner in order to have comparable results. Assessment of pain pre- and postoperatively with a pain evaluating model e.g. VAS is of great importance in understanding the amount of achieved pain relief. A quality of life measurement may identify patients who fail to sustain a total pain control but still gain improvements post treatment.

**Conclusions**
Cryosurgery is a minimal invasive procedure and the reported adverse effects following surgery are minor and reversible. There is a pain relieving effect in some patients diagnosed with trigeminal neuralgia undergoing cryosurgery though the effectiveness of the cryosurgical procedure needs to be further assessed.
References

1. National Institute of Neurological Disorders and Stroke (NINDS),


**Acknowledgements**

We would like to thank the Oral and Maxillofacial Surgery clinics participating in our investigation of praxis.
### Tables

**Table 1 – Medline search**  
Search strategy in Medline, and number (n) of publications retrieved

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<td>#7 AND #15</td>
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Table 2 – Web of Science search
Search strategy in Web of Science, and number (n) of publications retrieved

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Table 3 – Inclusion and exclusion criteria
Inclusion and exclusion criteria of studies of patients diagnosed with trigeminal neuralgia receiving cryosurgery

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<td>Clinical study</td>
<td>Case reports</td>
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<td>Patients diagnosed with tic douloureux or trigeminal neuralgia</td>
<td>Patients previously treated with injections or surgery for trigeminal neuralgia</td>
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<tr>
<td>Surgical treatment with cryosurgery</td>
<td>Multiple sclerosis, neoplasm or trauma induced trigeminal neuralgia</td>
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<td>Post treatment pain evaluation</td>
<td>Pain evaluation post treatment less than 3 months</td>
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<td>Peripheral appliance of the cryoprobe</td>
<td>Studies not written in English, Swedish, Norwegian or Danish.</td>
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<td>Usage of diagnostic blockade to verify diagnosis</td>
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### Table 4 - Results
Included studies, extracted data and outcomes of cryosurgery in treated patients. *Synonym to trigeminal neuralgia*

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<th>First Author</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
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<th>Diagnosis</th>
<th>Freeze thaw cycle and temperature</th>
<th>Follow up</th>
<th>Pain relief</th>
<th>Adverse effects</th>
<th>Study quality according to STROBE (max. 22)</th>
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<td>1976</td>
<td>England</td>
<td>Prospective</td>
<td>6</td>
<td>Tic doloureux*</td>
<td>2x2 min -60°C</td>
<td>&gt;3 months</td>
<td>Median duration: 21 days</td>
<td>None described</td>
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<td>Barnard</td>
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<td>England</td>
<td>Prospective</td>
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<td>Tic doloureux*</td>
<td>2x1 min -60°C</td>
<td>3 years</td>
<td>Median duration: 235 days</td>
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<td>Prospective</td>
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<td>Trigeminal neuralgia</td>
<td>2x1.5 min -18 months to 3 years</td>
<td>Median duration in 7 out of 11 patients: 15 months</td>
<td>Sensory loss, small oedema</td>
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<td>England</td>
<td>Prospective</td>
<td>39</td>
<td>Trigeminal neuralgia</td>
<td>3x2 min -120°C</td>
<td>4 years</td>
<td>1 year: 50% pain free</td>
<td>Sensory loss, Pain migration</td>
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<td>Retrospective</td>
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<td>Trigeminal neuralgia</td>
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<td>5 years</td>
<td>&gt;1 year: 41%</td>
<td>Sensory loss, Pain migration, Post-op infection</td>
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<td>2x1.5 min -120°C</td>
<td>1 to 3 years</td>
<td>1 year: 32% pain free</td>
<td>Sensory loss, Small oedema</td>
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Figures

Figure 1 – The trigeminal nerve
Retrieved from AnaesthesiaUK (32)

![Figure 1 - The trigeminal nerve](image)

Figure 2 – Cryosurgery of the mental branch of the trigeminal nerve
In courtesy of Sten Isaksson, Halland hospital, Halmstad, Sweden

(a) Mental foramen with the mental nerve exposed

(b) Appliance of a cryoprobe to the mental nerve
Figure 3 - Flowchart

Literature search in Medline and Web of Science. The included publications from the search in Web of Science were duplicates to included publications retrieved in Medline.

Web of Science

- Excluded abstracts n = 13
- Excluded fulltext n = 8
- Abstract n = 24
- Fulltext articles n = 11
- Included original articles n = 3 (duplicated in Medline)
- Reference lists handsearch n = 9
- No abstract n = 7

Medline

- Abstract n = 32
- Fulltext articles n = 13
- Included original articles n = 4
- Excluded abstracts n = 19
- Excluded fulltext n = 9

Included articles n = 2

Total included non-duplicated articles n = 6