ROLE OF CRYOTHERAPY IN TRIGEMINAL NEURALGIA WITH CERTAIN MODIFICATTIONS: A LONG TERM PROSPECTIVE STUDY

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Abstract

Objective- This study entails application of cryosurgery with certain modifications as a treatment modality for patients diagnosed with trigeminal neuralgia refractory to pharmacological treatments.

Study Design- 49 patients diagnosed with trigeminal neuralgia were treated with cryosurgery which included 13 infra-orbital, 18 inferior alveolar nerve, 17 mental nerve, and 1 supra-orbital nerve with closed, curved type of cryoprobe with nitrous oxide, at temperature of -98degree C, and pressure 70 kg/cm^2 or 100 psi.

Results- Pain free interval was observed to be less than 18 months for 4.08% patients, in the range of 36 to 40 months for 48.97% patients, 48-52 months for 32.65% patients and more than 52 months in 14.28% patients. All the patients experienced loss of fine and crude sensation for a time period of 6 to 24 months.

Conclusion- Cryotherapy can be deduced to be a safe and economic modality which can be repeated if required.

INTRODUCTION.

Trigeminal neuralgia (TN) or Tic- Douloreux is defined by The National Institute of Neurological Disorders and Stroke (NNDS) as “a chronic pain condition that causes extreme, sporadic, sudden burning or shock- like face pain.” It is characterized by paroxysomal pain in interval of few seconds to minutes. [1] The severity of pain is both physically and mentally incapacitating urging the patient towards suicidal attempts.[1,2] There is lack of certainty regarding the etiology and pathophysiology of this distressing condition. It may be associated with tumors and vascular anomalies that compress the trigeminal nerve root, multiple sclerosis or idiopathic. [3] Focal demyelination at the site of compression may allow electrical spread of excitation between adjacent sensory axons (ephaptic transmission).[4] In case of trauma, regenerating nerve fibers become relatively depolarized and physiologically more excitable.[5] Thereby they produce spontaneous action potentials that may evoke release of sustained after discharges. [4] Most popular and accepted criteria to diagnose TN is mentioned by White and Sweet. The criteria emphasize 5 major clinical features including 1. paroxysmal pain, 2. presence of trigger zone, 3. unilateral presentation, 4. pain confined to trigeminal distribution and 5. normal sensory examination.[6] Diagnosis in most of the cases is made by clinical history or response to anti neuralgic drugs. Contrast MRI are useful in screening for CPA tumor and compression of trigeminal root.[7] Medical treatments like carbamazepine, gabapentin, phenytoin, baclofen and lamotrigine are the 1st choice for management.[8] Side effects like megaloblastic anemia, skin reactions, gastric intolerance, hepatotoxicity are frequently associated with anti-neuralgic drugs.[9] Refractory to medical treatment and drug intolerance open the door for surgeon. Surgery can be performed peripherally

on nerves or centrally in the posterior fossa of the skull. The central procedures involve separation of the trigeminal ganglion from surrounding compressing arteries, veins or tumors that include micro- vascular decompression, electrical induced heating of the ganglion, compression of the ganglion or radiation of the ganglion (gamma- knife radiosurgery).[7] Peripheral surgical techniques are less invasive, include injection of alcohol, glycerol or local anesthetic agents in the peripheral branches of the trigeminal nerve, peripheral neurectomy or cryotherapy.[10] Centrally acting treatment like microvascular decompression may lead to eighth nerve problems (in 11% of patients), intra-cerebellar hematoma and has 1% mortality risk.[11] Percutaneous radiofrequency thermocoagulation is ineffective in the long term unless total anesthesia in the affected area is induced with 23% recurrence rate.[10] Patients with compromised medical status may be unfit to undergo any procedure under general anesthesia. These drawbacks of invasive procedures lead to the indulgence in peripheral procedures for correction of trigeminal neuralgia. Peripheral procedures like alcohol injection, peripheral neurectomy, radiofrequency thermoneurolysis of peripheral nerves have shown a positive outcome in terms of loss of pain, but the duration of action has been noted to be short accompanied with complications like neuroma formation and loss of sensory function.[12] This paper will be highlighting the role of cryotherapy in patients of trigeminal neuralgia with certain modifications in technique, to improve quality of life by achieving long pain free interval on long term follow up.

MATERIAL AND METHODS

49 patients referred from department of medicine as diagnosed case of TN, refractory to medicinal treatment were included in this study and treated with cryosurgery between 2010 to 2013 with follow up maintained till date. Any other central or peripheral cause of neuralgia like CP angle tumor, microvascular nerve compression, pathology, sinusitis or malignancy were ruled out with Contrast MRI and routine radiograph like orthopantamogram and PNS. In present study female: male ratio was 16:33, left versus right side ratio was 38:11, age range between 45 to 60 years were observed. Diagnosis was confirmed with white and sweet Criteria and diagnostic nerve block. To confirm the affected nerve all patients who were refractory to antineuralgic drugs were instructed to discontinue anti-neuralgic drug 24 hours prior to diagnostic block. 2 % lignocaine with adrenaline was injected in affected nerve. Once patient became pain free, long acting anesthesia that is 0.5% bupivacaine was used to know the pain free interval and to rule out involvement of any other nerve, on three consecutive days to identify the affected branch. Patients were prescribed tramadol hydrochloride and paracetamol for pain management. Patient suffering from Trigeminal Neuralgia of more than one nerve, medically compromised and suspected other causes of pain were excluded from the study. All patients were treated under local anesthesia except three in which inferior alveolar nerve was involved, were treated under general anesthesia. Infra-orbital nerve was exposed through intra-oral vestibular incision. (Fig.1) Mental nerve by lower vestibular incision for dentate patients or crestal incision with anterior release in edentulous patients, which prevents direct nerve injury when it is highly positioned due to crestal bone loss. (Fig. 2) Supra-orbital nerve was exposed by upper eye brow

incision and inferior alveolar by modified Ginwalla's incision which is an inverted y shape incision over ascending border of ramus of mandible and in some of the cases in lieu of access to the nerve, temporalis crest was trimmed. In all the cases nerve was exposed as it emerges from foramen except in case IAN which was exposed before entering to foramen, where 5-7 mm length of nerve was bluntly dissected from surrounding tissue. (Fig. 3) Certain modifications were performed which were multiple scoring with 15 no. blade on epineurium, application of lubricant jelly over the exposed nerve which allows the ice to stay in close proximity to the nerve thereby increasing the depth of penetration and extending the effectiveness and duration of cryo-analgesia. (Fig. 4) Three freezing cycles were delivered in all nerves. Depending on the thickness of the nerve freezing time was varied, it was 5 minutes for inferior alveolar nerve which was relatively thicker and 3 minute for supra-orbital, infra orbital and mental nerve. (Fig. 5) Thawing period of 5 minute was maintained in all the nerves. Wound was meticulously closed with 3-0 silk and post operatively only antibiotics and analgesics were prescribed for 5 days. No anti-neuralgic drug was prescribed. Patients were recalled after 48hrs, 7 days for suture removal and assessment of neurological deficit, 1 month and 3 months consecutively thereafter. Patients who presented with recurrence of pain were retreated with cryosurgery and follow up was maintained. This study has been conducted in accordance with the World Medical Association Declaration of Helsinki. All procedures used in this research were approved by the Ethical Committee with reference number: SDC/ CER/2010/132.

ARMAMETARIUM

In our study closed, curved type of probe was used and the cooling system(Basco.co) functioned with nitrous oxide, as a refrigerant at temperature of -98degree C, and the pressure was 70 kg/cm^2 or 100 psi.

RESULTS

Total 49 nerves were treated with cryotherapy. Out of 49 nerves, 13 were infra-orbital, 18 were inferior alveolar nerve, 17 were mental nerve, and 1 patient was treated for supra-orbital nerve. All our patients got relief from sharp, shooting pain in the first visit. Post-operative sequel like swelling, pain and trismus (in cases of IAN) was evident in all the patients but recovered with warm saline rinses and physiotherapy. All patients developed loss of response to fine as well as crude touch which was seen to recover within 4-6 months. Response to fine touch was lost in all the patients for 20-24 months. Pain free interval was observed to be less than 18 months for 4.08% patients, in the range of 36 to 40 months for 48.97% patients, 48-52 months for 32.65% patients and more than 52 months in 14.28% patients (Table no 1). Patients who reported with pain were retreated by cryotherapy and showed similar results.

DISCUSSION

Trigeminal Neuralgia affects 4-13 per 100 000 people each year, authors observed an incidence of around 20 in 10,000 patients.[4] In a systemic review by Toledo and colleagues it was seen that women were more commonly affected with age range of 37 to 67 years.[13] In current study also females were affected more commonly than male and in the age range of 45 to 60 years. In a study by Zakrzewska et al right side of face was involved in 57% of cases, but we could appreciate only 22% cases in which right

side of face was affected.[14] The incidence gradually increases with age, rarely individuals younger than 40 years of age are affected. Katusic et al report the incidence of trigeminal neuralgia and states that in 35% cases maxillary branch of trigeminal nerve was involved in 29% cases the mandibular branch, 19%cases involved both and only 4% involved ophthalmic branch.[15] In present study 71.42%cases involved mandibular nerve, 26.53% maxillary and only 2.04% ophthalmic branch. The diagnosis of trigeminal neuralgia remains an arduous job for any clinician. The conditions followed to include patients in the study involved White and Sweet criteria, diagnostic block, contrast MRI scan to rule out centrally lying etiological lesion, and patients who were refractory to anti-neuralgic drugs.[7] In present study compression of trigeminal nerve due to cerebellopontine angle tumor was found in none of the cases but compression by middle or posterior cerebellar artery was seen in 16% cases. Out of these 8 patients 2 had pain free interval of less than 18 months and rest in range of 36 to 40 months.

Numerous studies in the past have been performed to achieve longer pain free period by varying the operative parameters. In a study performed by Barnard et al in 1981 on 24 patients suffering with trigeminal neuralgia who were treated with cryosurgery while maintaining temperature in range of -60 to -80 and 2 cycles of 1 min freeze-thaw period had a mean pain free interval of 186 days.[16] Goss et al in 1984 performed cryoneurotomy in 11 cases with 2 x cycles of 90 second freeze and 2 min thaw and found the mean pain free interval to be 15 months.[17] It can be postulated that better result in this study can be because of longer freezing and thawing time. In 1986 Zakrzewska performed cryotherapy at temperature of -120 and repeated 2-minute freezing and 5-minute thawing cycles 3 times with 84% patients having pain free interval

more than a year and 32% more than 4 years. This longer duration of pain relief can be attributed to lower (-120) temperature, longer period of freezing and thawing cycles and three-time repetition of freezing cycles.[10] Another study by Pradel et al in 2002 on 19 patients, maintained temperature between -40 to -120 with 2 cycles of 90 seconds freeze and 40 seconds thaw, observed return of pain within 6-8 months.[9] Study performed by Pradel achieved shorter pain free period compared to Zakrzewska which can be due to decreased duration of freezing and reduced no. of repetition of cycles.

Cryosurgery as a treatment modality functions towards symptomatic management by providing relief from pain, hence its efficacy can be improved by prolonging the duration of pain relief. In the current study 96% patients had relief from pain for more than 3 years and 56.8% more than 4 years which is considerably better than studies performed in the past and can be caused by certain modifications which were carried out -:

1. **Use of curved cryoprobe**

   Cryoprobe are effective surgical tools for application of cold temperature to the required surgical field. Cryoprobes of different designs have been introduced varying in their size and shapes. Rothenborg illustrated the variations that can be achieved when altering the pressure and diameter of the cryotip. He stressed upon the importance of contact between the nerve and tip which guided us to use a curved end cryoprobe.[18]

2. **Maintaining optimum temperature, and pressure throughout the surgical procedure**

It has been observed that when the freezing temperature is maintained at -20°C no significant change was observed in function and morphology of nerve but when further lowered between - 60°C to -100°C myelinated fibers were injured selectively, with complete recovery in 60 days. Further cooling at temperatures between - 140°C to - 180°C helped achieve complete nerve fiber necrosis with subsequent incomplete regeneration. [19] Hence the temperature in our study was maintained at -98°C.

3. Scoring of the epineurium

Bradley et al discusses the loss of regeneration capacity when there is breach in the anatomic continuity of nerve which provoked the author to perform scoring of the nerve. Since regeneration is likely to be poor or not at all the pain free interval can be prolonged with this modification. [20]

4. Application of petroleum jelly around the nerve before introduction of cryoprobe

Rothenborg studies also depicts the better performance achieved when moisture was present around the freezing nerve by providing a better contact.[18] It was further ascertained by a study done by Bradley and fisher by using thermograms when freezing was done with or without a jelly around nerve. It revealed better freezing with application of jelly owing to reduced thermal resistance between nerve and cryotip. [21] In present study scoring of epineurium and application of

petroleum jelly seems to be one of the influencing factors for long duration of pain free interval in majority of cases.

5. Delivery of 3 cycles of 3-minute freezing (5 min for inferior alveolar nerve) and 5-minute thawing to each nerve.

The diameter of nerve may be predicted to play a pivotal role on freezing to the core of nerve fibers, for which the freezing time for thicker nerve like inferior alveolar nerve is kept longer than the rest of the nerves. [22] It has been seen that the estimated cross section area of supra orbital foramen around 1.79 mm, infra orbital nerve - 2 mm^2 in the infra orbital canal and 0.4mm^2 as it exists the infra orbital foramen, mental nerve - 1.18 ± 0.27 mm^2, inferior alveolar nerve - 1.64 ± 0.27 mm^2 in third molar region with largest diameter of 2.4 ± 0.4 mm at the lingula. [23,24] It can be clearly appreciated that the inferior alveolar nerve is thicker than the others hence longer freezing time was applied to it.

We followed the basic protocol of fast cooling to a lethal temperature followed by slow thawing, and repetition of the freeze–thaw cycle similar to a regimen followed by Zakrzewska in 1986. [25,10] We performed 3 cycles of 3-minute freeze (5 min for inferior alveolar nerve) followed by a 5-minute thaw. The importance of longer thawing can be explained by process of recrystallization of ice within the cell during thawing which primarily contributes to cellular injury.[25] It has been proposed that block of energy-dependent calcium excluding mechanisms followed by an influx of calcium ions initiates axoplasmic degeneration and presents with longer time for pain to resurface. [26]

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CONCLUSION

Various treatment modalities including surgical and medicinal have been mentioned in the literature, each having its own advantages and limitations. Cryoanalgesia is a simple, safe and cost-effective method in which integrity of the nerve is maintained and also avoids major surgical procedures in management of trigeminal neuralgia. Certain modifications to the conventional cryosurgical technique have shown to improve the quality of life by increasing the pain free period for longer duration with minimal adverse effects. Therefore, if given choice between two treatment methods, simplest method is always the best if all else is equal.

Statement of Clinical Relevance

The application of cryosurgery with certain modifications has been highlighted in this study in 49 patients with long term follow up. A pain free period ranging from at least 18 to more than 52 months was recorded.

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LEGEND

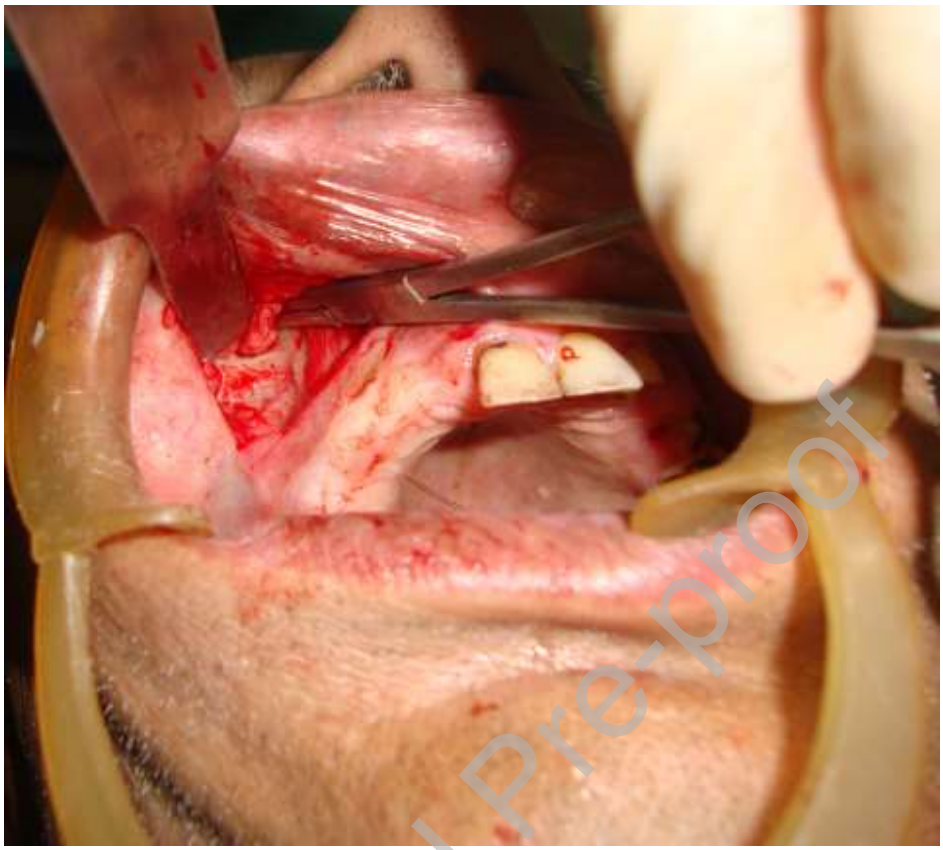

Fig. 1 - Exposure of infra orbital nerve

Fig. 2 - Exposure of right mental nerve

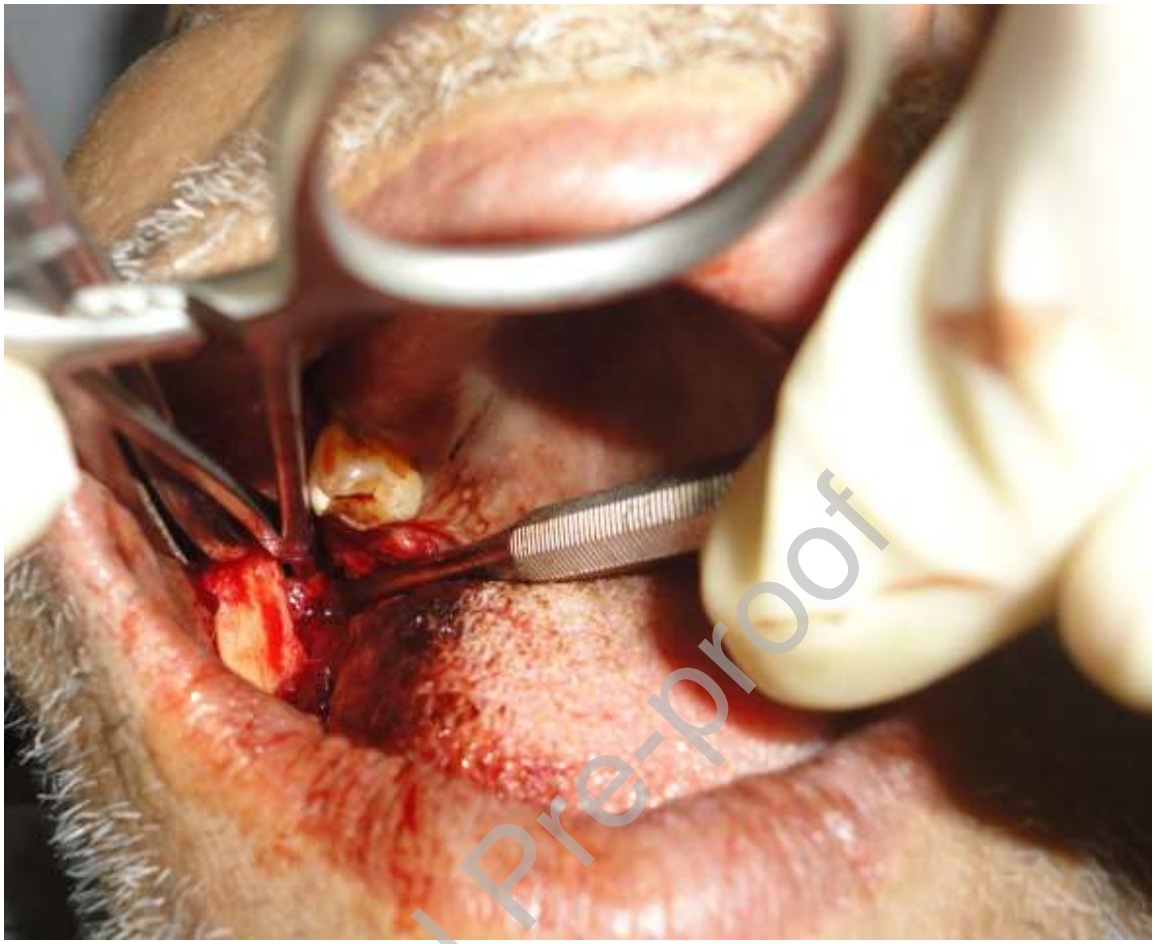

Fig. 3 - Exposure of inferior alveolar nerve

Fig. 4 - Scoring of epineurium

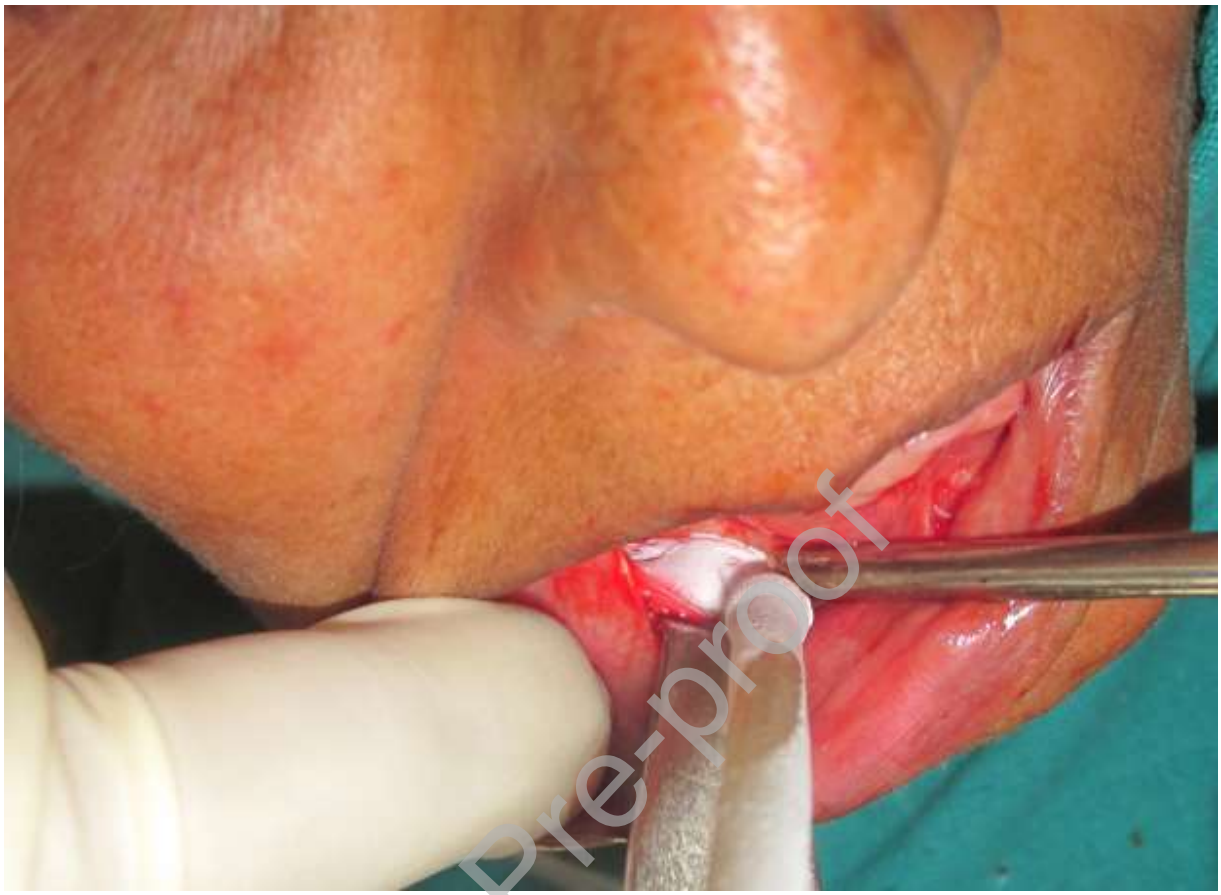

Fig. 5 - Freezing cycle with curved probe

Table 1- Pain free interval

NERVE	**TOTAL No. of Nerves**	**Pain free period**			
		18 MONTHS	**36-40 MONTHS**	**48-52 MONTHS**	**MORE THAN 52 MONTHS**
INFERIOR ALVEOLAR	18	1	9	7	1
MENTAL	17	1	8	5	3
INFRA ORBITAL	13		7	4	2
SUPRA ORBITAL	1				1
TOTAL- 49					