



ISSN Print: 2394-7489
ISSN Online: 2394-7497
IJADS 2022; 8(2): 548-552
© 2022 IJADS
www.oraljournal.com
Received: 03-03-2022
Accepted: 09-04-2022

Dr. Prajesh Dubey
Professor, Department of Oral
and Maxillofacial Surgery,
Subharti Dental College &
Hospital, Swami Vivekanand
Subharti University, Meerut,
Uttar Pradesh, India

Dr. Apoorva Mowar
Professor and Officiating Head,
Department of Oral and
Maxillofacial Surgery, Subharti
Dental College & Hospital,
Swami Vivekanand Subharti
University, Meerut, Uttar
Pradesh, India

Dr. Sonam Khokhar
Post Graduate Student,
Department of Oral and
Maxillofacial Surgery, Subharti
Dental College & Hospital,
Swami Vivekanand Subharti
University, Meerut, Uttar
Pradesh, India

Corresponding Author:
Dr. Sonam Khokhar
Post Graduate Student,
Department of Oral and
Maxillofacial Surgery, Subharti
Dental College & Hospital,
Swami Vivekanand Subharti
University, Meerut, Uttar
Pradesh, India

Role of cryosurgery in maxillofacial lesions: A literature review

Dr. Prajesh Dubey, Dr. Apoorva Mowar and Dr. Sonam Khokhar

DOI: <https://doi.org/10.22271/oral.2022.v8.i2h.1556>

Abstract

Cryosurgery has the ability to produce very low temperatures which causes tissue destruction. It has been found to be effective for oral cavity lesions of the infants, elderly patients and also of the immunocompromised patients. Cryosurgery is a very safe, easy to perform, and relatively inexpensive technique for treating various oral injuries on an outpatient basis. It is an atraumatic form of therapy compared to conventional surgery. Liquid nitrogen spray or cryoprobe has been used alone or in combination with other surgical methods in various types of oral lesions. According to various studies and literature, cryosurgery has been found to be effective for the treatment of refractory trigeminal neuralgia and TMJ pain, as it provides longer pain free interval than the other treatment modalities. It has been utilized as an effective method for the treatment of benign conditions like gingival pigmentation, inflammatory papillary hyperplasia, mucocele; premalignant conditions like leukoplakia, lichen planus and as a palliative therapy for malignant conditions like erythroplakia, squamous cell carcinoma. In hypertrophic scars, as an adjuvant therapy after enucleation for odontogenic lesions like ameloblastomas, keratocysts and for vascular lesions like capillary hemangiomas it has been found to be beneficial.

Keywords: Cryoanalgesia, cryosurgery, freezing, thawing, oral lesions

Introduction

Surgical modality is the gold standard for the treatment of oral lesions, but as science evolved there was a need of atraumatic, bloodless procedure, which could give, same or better results than surgical modality and cryosurgery is one of these modalities^[1].

Cryosurgery is a method of local tissue destruction by freezing in situ. "Cryosurgery" is derived from the Greek word "Kryos," that is, frost, thus literally meaning frost surgery^[2].

History of cryosurgery

The Egyptians were the first to use cold for inflammation and trauma^[2]. In the 17th century, Robert Boyle discovered that cells could be killed by freezing^[3]. In 1845, James Arnott was the first to report the therapeutic use of low temperatures (-18 °C to -24 °C)^[4] in malignant disease by means of a salt/ice mixture applied to breast neoplasms. He found that this temperature is adequate to freeze tumors, along with a resultant decrease in size, reduction in drainage and improvement in pain. He used it as a palliative for terminal cancer patients and for neuralgia^[5]. In 1877, Louis Cailletet^[6] liquefied oxygen and carbon monoxide by cooling them to -29 °C and compressed them to 300 atm. James Dewar^[7] manufactured a vacuum flask for storing liquefied gases such as oxygen, nitrogen and hydrogen in 1892.

In early 1960s, the role of cryosurgery was considered to be effective in oral surgery. Amaral *et al.*^[8] applied cotton soaked in liquid nitrogen for 12-30 sec to treat hyperplastic tissue and found complete shrinkage of tissue after treatment at weekly interval for two to four times. In 1981 Mac Donald *et al.*^[9] advised cryosurgery for the treatment of lichen planus, hyperplasia of palate, angiomas, and leukoplakia. In 1981, Barnard^[10] found that cryotherapy produces an extended and reversible nerve block in the management of chronic pain and postoperative pain. In 1988 Goss^[11] found that cryofreezing of the peripheral nerve supply of the temporomandibular joint does result in excellent short term pain relief for selected cases but in the longer term recurrence is likely.

Cryogenics

The commonly used cryogenics include liquid nitrogen (-196 °C), nitrous oxide (-89 °C), solidified CO₂ (-78 °C) (dry ice CO₂ snow), chlorodifluoromethane (-41 °C), dimethyl ether and propane (-24 °C, -42 °C) [12].

System of cryosurgery

The application of cryogenics can be done via two systems: open system and closed system. Closed system involves the use of probes and nitrous oxide while open system involves the use of a liquid nitrogen spray or a cotton tip. Spray techniques are useful in intraosseous cavities after curettage, small skin cancers and extensive dermatological lesions to prevent recurrence. The nitrous oxide technique is useful for the treatment of various benign and malignant lesions of the oral cavity. Cryoprobes follow the principles of Joule-Thompson expansion which enable substances to undergo a fall in temperature when passing from a high pressure area to a lower pressure area. When nitrous oxide is released from the high pressure inside the cryoprobe to the low pressure cryo tip, the drop in temperature allows tissue freezing. Liquid nitrogen sprays and cotton swabs are more accessible to clinicians but they are not suitable for use in the oral cavity. Their disadvantage is lack of control over the temperature achieved within cells and the area of freezing, which makes them hazardous to use intraorally. In addition, the rapid evaporation of liquid nitrogen from cotton swabs requires numerous applications to wounds. A more controlled and profound depth of freezing can be achieved with a nitrous oxide cryoprobe due to direct contact between the cryogen and tissue [13].

Mechanism of cryosurgery

Tissue destruction is a multifactorial process following cryotherapy. Tissue death is the result of a combination of direct cellular effects, such as formation of ice crystals, protein denaturation, cellular dehydration, from ischemic infarction resulting from failure of microcirculation and disruption of cell membranes. Vascular stasis reinforces the direct lethal effect. As the lesion undergoes repetitive freeze and thaw cycles, accumulation of damage occurs. Cryogenic damage cannot be distinguished from the original tissue immediately after treatment. In following days, latent damage is produced which progresses to severe damage and cause subsequent necrosis to the tissues. As the temperature drops during the freeze cycle, extracellular water undergoes crystallization. At low temperature, membrane lipid hardens decreasing cell resistance to shrinkage. The electrolyte concentration increases as extracellular stores of water diminish. Intracellular water moves out of the cell in order to counteract this concentration gradient and this water becomes involved in the crystallization process. In addition, the intracellular ice formed remains trapped in the cell membrane. As a result of these processes, intracellular electrolytes reach toxic levels and become lethal to the cell. Cells at the periphery of the cryolesion will take up excess electrolytes during a slow thaw cycle. Water then enters the cell to equalize this gradient and cause swelling and lysis. Recrystallization may also contribute to cellular damage, but if cells are thawed rapidly this phenomenon may be avoided [13].

Effect of cryosurgery on various lesions

In 1916 Trendelenberg [14], described the structural changes that occur in nerve tissue after freezing and found a good

recovery without any scar and neuroma formation with evidence of regeneration. Whittaker [15] reported degenerative changes in the axon and myelin sheath beginning immediately on thawing a nerve which had been frozen to -70 °C for 1 minute but unmyelinated nerve showed minimal changes. In contrast, Wener *et al.* [16] reported that the signs of degeneration were seen at 24 hours including the unmyelinated fibers. Sunderland [17] stated that maintaining endoneural continuity is necessary for nerve repair and regeneration. Carter *et al.* [18] after applying a temperature of -100 °C on motor nerve found complete loss of function with evidence of regeneration beginning at 14 days and got completed by 25 days.

Beazley *et al.* [19] using a temperature of -40 °C on facial nerve and -70 °C on recurrent laryngeal nerve reported that recovery began to occur at 6 weeks and got completed by 9 weeks.

Zakrzewska [20] performed cryotherapy in 39 patients for the management of PTN using liquid nitrogen at temperature of -120 °C and repeated 2 minute freezing and 5 minute thawing cycles 3 times. The normal sensation in all the patients returned within 3 months and 84% patients were found to have a pain free interval of more than one year while in 32% patients it was more than 4 years [20].

Pradel *et al.* [21] using liquid nitrogen through a hand spraying device at a pressure of 0.4mPa in 19 patients for the treatment of genuine TN, maintaining the temperature between -40 °C to -120 °C with 2 cycles of 90 seconds freeze and 40 seconds thaw observed returning of pain within 6-12 months in 68% patients. Study performed by Pradel *et al.* achieved shorter pain free period due to decreased duration of freezing and reduced no. of repetition of cycles [21].

Over a century cryosurgery has been used as a treatment modality for various oral lesions irrespective of conditions of being benign, premalignant or malignant.

Shirazi *et al.*, [22] in their study on 15 patients of melanin pigmentation of the anterior segment of gingiva of both maxilla and mandible using liquid nitrogen cotton swab 4mm in diameter in 3 cycles of 20 sec freeze found the appearance of the gingiva was normal in color in all the patients without any post-operative scar formation, pain or associated complications [22].

Yeh [23] treated 15 patients with oral melanotic macules on the vermilion borders of the lips using liquid nitrogen cotton swab of 5 mm to 10 mm in diameter for 10-15 seconds and found that melanotic macules disappeared 1 week after cryosurgery without any postoperative pain, hemorrhage, infection, or scarring [23].

Getter and Perez [24] in their study on 12 patients used 2 cycles of liquid Freon cryoprobe for 45 sec over the hyperplastic tissue at a temperature of -50°C to -60 °C. Several visits were needed to treat the entire hyperplastic tissue. They postulated that cryosurgery is an effective, painless method for the removal of inflammatory papillary hyperplasia with no postoperative or operative bleeding and little postoperative discomfort to the patients [24].

Borges *et al.* [25] treated 12 patients of inflammatory papillary hyperplasia by direct application of liquid nitrogen using a 6 mm closed probe. Two 60 sec treatment applications were performed, and thawing was allowed to proceed for 2 minutes between two consecutive freeze-thaw cycles. They reported that cryosurgery is an effective therapy only for up to 12 mm long pedunculated hyperplasia [25].

Toida *et al.* [26] treated 18 patients with mucocoeles of lower lip and tip of the tongue by direct application of liquid nitrogen

with a cotton swab of 5-15 mm in diameter according to the size of the lesion with moderate pressure. He applied a freezing time of 10–30 sec/cycle and thawing period were double the freezing time applied. Only after complete thawing was subsequent freezing applied. All lesions disappeared completely in 2–4 week time without scarring [26].

Yeh [27] treated 36 mucocele in 33 patients using liquid nitrogen cotton swab of 5-20 mm diameter corresponding to the size of the lesion with a freezing time of 30-50 sec per cycle and thawing period of 30-60 sec per cycle. Secondary treatment was performed after 1-2 week if any residual lesion remained. There were relapses in two patients with a rate of 5.6% who were also treated with cryosurgery to achieve complete resolution. All patients recovered by second intention [27].

Prasad *et al.* [1] treated 20 mucocele patients using liquid nitrogen cotton swab with little pressure. The freezing time was 10-30 seconds per cycle, followed by a thawing period of twice the freezing time for approximately 60 seconds. They reported complete resolution of the lesion without any discomfort or recurrence [1].

Use of cryosurgery as a treatment modality for leukoplakia dates back to 1970 when it was used by Leopard.²⁸ He used two freeze-thaw cycles of up to one and half minute depending on the site and thickness of the lesion and treated 40 patients of which two failed to respond [28].

Sako *et al.* [29] treated 60 patients with leukoplakia of oral cavity using liquid nitrogen cryoprobe with a probe tip temperature of -120 °C gave the recurrence rate of cryosurgery on leukoplakia as 20% [29]. Poswillo [30] emphasized the use of leukoplakia delineation with toluidine blue dye before application of cryo to provide an adequate freezing cycle for the entire patch region [30].

Lin *et al.* [31] treated 60 oral leukoplakia lesions by cryogen cryotherapy. 4 or 5 consecutive freeze – thaw cycles were performed with a freezing period of 7 to 10 sec and thawing period of at least 20 seconds. For small oral leukoplakia lesions spray was used while for medium or large oral leukoplakia lesion, a brush or spiral spray was used to deliver the liquid nitrogen. Complete regression with little or no scar formation after an average of 3.1 + 1.3 (range, 1– 6) cryotherapy treatments with cryogun were observed in all 60 oral leukoplakia lesions [31].

Chen H M *et al.* [32] treated 72 patients using liquid nitrogen spray for 7-10 sec onto the lesional surface to form an ice ball or field which extended 2–3 mm beyond the visible pathologic border of the lesion. The frozen field was then allowed to thaw for at least 20 sec. Freeze – thaw cycles were repeated for four-five times and it was observed that all 72 lesions showed complete regression with little or no scar formation after an average of 3.3 + 1.3 (range, 1-7) cryogun cryotherapy treatments [32].

From the various studies, it was found that, the recurrence rate for local excision by using scalpel and laser varies from 10–34%, and recurrence rate for cryosurgery varies from 13–25% which suggests that cryosurgery is also an effective method in management of leukoplakia as compare to other treatment modalities.

Narula and Malik [33] treated ten patients of oral lichen planus with cryosurgery using nitrous oxide system by applying two freeze-thaw cycles. Freezing time was one and half minute followed by a 3 minute thaw. Two of his patients presented a relapse. They suggested that cryosurgery is a good treatment modality atleast a palliative therapy for oral lesions of lichen planus [33].

Amanat *et al.* [34] compared cryosurgery treatment and steroids for thirty patients with bilateral OLP lesions. One unilateral lesion was randomly selected from each patient for a single cryotherapy session with nitrous oxide and the lesion on the other side received 0.1% triamcinolone acetone ointment in orabase. At the end of treatment, they found that nitrous oxide cryosurgery was as effective as the application of steroids. However, in patients with underlying systemic conditions that contraindicate steroid use, cryosurgery is the best treatment option [34].

Hausamen [35] treated 20 patients with oral squamous cell carcinoma and stated that cryosurgery can only be used for locally extensive superficial lesions but not suitable for deep infiltrating carcinomas [35].

Gage [36] treated 50 patients of oral and oropharyngeal carcinoma by using liquid nitrogen cryotherapy. Among them 39 patients were primarily curable and 11 patients are those who are resistant to radiotherapy, in whom the location of lesions are in areas which are difficult to excise and there is presence of severe cardiopulmonary disease. Among 39 patients, 9 patients died early post operatively. In the remaining 30 patients, cryotherapy fail to cure the primary lesions and the lesions recurs within 6 months of treatment. In 11 patients, where cryosurgery was used as a palliative therapy, survival of the patient was not prolonged but it only reduces size of the tumor and relieves pain. Thus cryotherapy can be used as a palliative therapy pre radiation and post chemotherapy in cases of inoperable poor prognosis oral carcinoma [36].

It is concluded that use of cryosurgery is successful for the initial stage of oral carcinoma as stated by various case reports but they are only a part of the history now. Cryosurgery is used as a palliative treatment option [37].

Study conducted by Leopard [28] using two freeze-thaw cycles one and half minute each reported complete regression of cavernous hemangiomas. Gongloff *et al.* [38] delivered nitrous oxide (–89°C) by a unique nitrous oxide cryosurgical apparatus, to deliver the freeze cycle for 127 sec in comparison to nitrogen system (60 sec) due to the temperature difference. Ten patients treated with nitrous oxide cryosurgery experienced minimal blood loss and discomfort [38].

Yeh [27] treated 20 hemangiomas (9 on the lips, 8 on the buccal mucosa, 2 on the tongue, and 1 on the maxillary vestibule) with cotton swab nitrogen system for 60–70 sec in 2–4 consecutive treatments and found no recurrence after a follow up period of 3 to 46 months (mean 26 months) [27].

Bekke and Baart [39] treated 22 patients suffering from hemangiomas (cavernous or capillary hemangiomas) and 5 patients suffering from lymphangioma present on tongue, lips, cheek, skin of the ala of nose and floor of mouth using cryosurgery. They found that sharply defined, superficial angiomas with a diameter not exceeding 3 cm can easily be treated by cryosurgery [39].

From the various studies it was concluded that capillary hemangioma responds better to cryosurgery, as compared to cavernous lesions. Lymphangiomas are rather less responsive to cryosurgery, particularly those which feature a moderate fibrous element.

Shepherd and Dawber [40] were the first who treated hypertrophic scar by using cryosurgery and they found 80% improvement along with high recurrence rate (33%). Mende [41], Zouboulis and Orfanos [42] used repeated surface/ spray cryosurgical sessions and showed remission between 68 – 81% with almost no recurrence (2%).

Shai *et al.* [43] treated 10 patients with 12 hypertrophic scars

and keloid using liquid nitrogen cryoprobe with a pressure of approximately 5 pounds per square inch, freezing period in range of 7-24 minute along with a thawing period of 2 to 3 minute. They found scar volume reduction of 51.4% after one session of intralesional treatment. After 18 month follow up period, they found no evidence of bleeding, infection, recurrence and permanent pigmentation^[43].

Zouboulis *et al.*^[44] treated 93 patients with 55 keloid patient and 38 keloid patient using nitrous oxide (-86 °C) and liquid nitrogen (-196 °C) cryoprobe of diameter not exceeding 1 cm for optimal contact with the lesional surface respectively. A freezing cycle of 30 seconds was used per lesion per session and, if necessary, the treatment was repeated every 20 to 30 days. Excellent responses were recorded in 30 subjects (32.3%), good responses in 27 (29.0%), poor responses in 27 (29.0%), while nine subjects (9.7%) did not respond at all. It was concluded that cryosurgery is the effective treatment modality for hypertrophic scars whereas minimal responsive to keloids^[44].

Pogrel M A (1993)^[45] in his study of 37 patients (25 keratocysts, 8 ameloblastomas, 2 giant cell lesions, and 2 myxomas of the mandible) used liquid nitrogen cryotherapy after enucleation. In four of the keratocysts, liquid nitrogen was applied by means of a probe placed into K.Y. jelly, filling the cyst cavity, but in all other cases, liquid nitrogen was used as a spray. For cryoprobe, 3 freezing of 1 minute and 5 minute of thawing between freezing and for spray 2 freezing of 1 minute and thawing of 5 minute between freezing was done. After a mean follow up period of 75 months, no recurrence was reported by the author in any of these lesions^[45].

Tonietto *et al.*^[46] treated 9 keratocystic odontogenic tumors using liquid nitrogen cryotherapy after enucleation by spray technique with 2 cycles of 1 minute freeze and 5 minute of thawing. They found zero recurrence rate with no pathological fracture^[46].

According to various studies, recurrence rate for the treatment of odontogenic lesions by enucleation alone was found to be 18 to 54.5%, by enucleation and curettage or ostectomy to be 18.2 to 20%, by enucleation and Carnoy's solution to be 11.4% and by enucleation and cryotherapy to be 0%. Carnoy's solution penetrates the bone to a depth of 1.54 mm while cryosurgery while penetration and margin of cellular necrosis produced by liquid nitrogen cryosurgery was shown to be average of 0.82 mm (0.51–1.52 mm). This concluded that use of cryosurgery after enucleation is found to be equally effective to Carnoy's solution for the treatment of odontogenic lesions.

Advantages of cryosurgery

It enables complete destruction of the selected volume of biological tissue regardless of being on the skin surface or within the body's organs. Cryodestruction enables quick healing, practically without leaving scars, while providing excellent cosmetic effect. Postoperative restorative period is shortened significantly, which allows for large increase in the number of patients. Minimal traumatic consequences, short time of operation, and the absence for the need of anesthesia, essentially broadens the circle of patients, for whom other surgical operations are contraindicated effectively makes cryosurgery to be the most prudent choice for treatment (for example, for the elderly or persons that is hypersensitive to medicaments, etc.)^[47].

Disadvantages of cryosurgery

Repeated cryosurgery procedures or an alternative method of

treatment is required when the volume of the lesion is beyond the freezing capacity of the available instrument. Cryosurgical healing occurs slowly. Extensive cryosurgery procedures can produce considerable scarring. After secondary intention healing, the loss of normal anatomy can lead to limited mouth opening, speech impairment, and prosthetic problems. If a biopsy is not performed before cryosurgery, the true nature of the lesion may not be established^[2].

Contraindications to cryosurgery

There are certain contraindications to the cryosurgery such as cold intolerance, cold urticaria, agammaglobulinemia, cryoglobulinemia, dysfibrinogenemia, Raynaud's and collagen diseases, gangrenous pyoderma, patients on hemodialysis or on immunosuppressive treatment, patients with platelet disorders or with multiple myeloma^[2].

Complications of cryosurgery

Complication categorized as immediate complication includes bleeding, blistering, edema, pain, vascular headache, vasovagal syncope. Delayed complications includes excessive granulation, infection is rare but possible with delayed healing, tendon rupture due to deeper freezing on extensor surface of fingers, ulceration. Permanent complications may include alopecia, atrophy, cartilage necrosis, hypopigmentation.

Future trends in cryosurgery

Cryotherapy cannot be regarded as a routine cancer treatment way because of the difficulty in recognizing the extent of cancer, limited freezing capabilities of cryosurgical apparatus in its present stage of development and possibility of survival of cancer cells following freezing. In order to overcome difficulties which were faced during conventional cryotherapy, nanoparticles are being used these days.

Nano cryosurgery introduce functional solution with nano particles into the target tissues which then serves as to either maximize freezing heat transfer, change ice-ball formation orientation or prevent healthy tissues from being frozen. Iron oxides magnetite (Fe₃O₄), maghemite (γ-Fe₂O₃) and MgO are perhaps the most popular nanoparticles because of their good biological compatibility^[48].

Conclusion

Cryosurgery has been utilized as an effective method for the treatment of benign conditions like gingival pigmentation, inflammatory papillary hyperplasia, mucocele; premalignant conditions like leukoplakia, lichen planus and as a palliative therapy for malignant conditions like erythroplakia, squamous cell carcinoma etc. Cryosurgery has been found to be effective for vascular lesions like capillary hemangiomas and in hypertrophic scars. Cryosurgery has been found to be beneficial as an adjuvant therapy after enucleation for odontogenic lesions like ameloblastomas, keratocysts etc.

References

1. Prasad M, Kale TP, Halli R, Kotrashetti SM, Baliga SD. Liquid nitrogen cryotherapy in the management of oral lesions: a retrospective clinical study. *J Maxillofac Oral Surg.* 2009;8(1):40-2.
2. Bansal A, Jain S, Gupta S. Cryosurgery in the treatment of orofacial lesions. *Indian J Dent Res.* 2012;23(2):297.
3. Rowell AG. Cryosurgery. *Aust Dent J.* 1976;21:1-2.
4. Theodorescu D. Cancer cryotherapy: evolution and biology. *Rev Urol.* 2004;6(4):S9.

5. Arnott J. Practical illustrations of the remedial efficacy of a very low or anesthetic temperature. I. In cancer. *Lancet*. 1850;2:257-259.
6. Papanelopoulou F. Louis Paul Cailletet: The liquefaction of oxygen and the emergence of low-temperature research. *Notes Rec. R. Soc.* 2013;67(4):355-73.
7. Wisniak J. James Dewar-More than a flask. *Indian J Chem Techn.* 2003;10:424-434.
8. Amaral WJ, Frost JR, Howard WR, Cheatham JL. Cryosurgery in treatment of inflammatory papillary hyperplasia. *Oral Surg Oral Med Oral Pathol.* 1968;25:648-54.
9. MacDonald RD, Pospisil OA. Comparison of experimental carcinogenesis in normal hamster cheek pouch and pouch treated previously by cryosurgery. *Br J Oral Surg.* 1981;19:24-8.
10. Barnard D, Lloyd J, Evans J. Cryoanalgesia in the management of chronic facial pain. *J Maxillofac Surg.* 1981;9:101-2.
11. Goss AN. Cryoneurotomy for intractable TMJ pain. *Br J Oral Maxillofac Surg.* 1988;26:26-31.
12. J sunitha. Cryotherapy—A review. *J Clin Diagn Res.* 2010;4(2):2325-2329.
13. Farah CS, Savage NW. Cryotherapy for treatment of oral lesions. *Aust Dent J.* 2006;51(1):2-5.
14. Trendelenburg W. Over long-lasting nerve elimination with safe regeneration capability. *J Exp Med.* 1917;5(1):371-4.
15. Whittaker DK. Mechanisms of tissue destruction following cryosurgery. *Ann R Coll Surg Engl.* 1984;66(5):313.
16. Wener RG, Pinkerton RMH, Robertson DM. Cryosurgical induced changes in corneal nerves. *Can J Ophthalmol.* 1973;8:548.
17. Sunderland S. *Nerve and Nerve Injury*, E. and s. Livingstone, Edinburgh, London, 1968, 131pp.
18. Carter DC, Lee PWR, Gill W, Johnston RJ. The effects of cryosurgery on peripheral nerve function. *J R. Coll. Surg.* 1972;17(1):25.
19. Beazley RM, Bagley DH, Ketcham AS. The effects of cryosurgery on peripheral nerves, *J Surg. Res.* 1974;16:23.
20. Zakrzewska JM, Nally FF. The role of cryotherapy (cryoanalgesia) in the management of paroxysmal trigeminal neuralgia: a six-year experience. *Br J Oral Maxillofac Surg.* 1988;26(1):18-25.
21. Pradel W, Hlawitschka M, Eckelt U, Herzog R, Koch K. Cryosurgical treatment of genuine trigeminal neuralgia. *Br J Oral Maxillofac Surg.* 2002;40(3):244-247.
22. Shirazi AS, Moeintaghavi A, Khorakian F, Talebi M. Treatment of gingival physiologic pigmentation in adolescents by liquid nitrogen cryosurgery: 24-month follow-up. *Int J Periodontics Restorative Dent.* 2012;32(4):e142-6.
23. Yeh CJ. Simple cryosurgical treatment of the oral melanotic macule. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;90:12-13.
24. Getter L, Perez B. Controlled cryotherapy in the treatment of inflammatory papillary hyperplasia. *Oral Surg Oral Med Oral Pathol.* 1972;34:178-86.
25. Borges HO, Munhoz EA, Machado RA, Silva DN, Martins MA, Filho MS. Clinical use of cryotherapy to treat oral inflammatory hyperplasia. *Int J Clin Dent Sci.* 2011;2:50-4.
26. Toida M, Ishimaru JI, Hobo N. A simple cryosurgical method for treatment of oral mucous cysts. *Int J Oral Maxillofac Surg.* 1993;22:353-5.
27. Yeh CJ. Simple cryosurgical treatment for oral lesions. *Int J Oral Maxillofac Surg.* 2000;29:212-6.
28. Leopard PJ. Cryosurgery and its applications to oral surgery. *Br J Oral Surg.* 1975;13:128-52.
29. Sako K, Marchetta FC, Hayes RL. Cryotherapy of intraoral leukoplakia. *Am J Surg.* 1972;124(4):482-4.
30. Poswillo DE. A comparative study of the effects of electrosurgery and cryosurgery in the management of benign oral lesions. *Br J Oral Surg.* 1971;9(1):1-7.
31. Lin HP, Chen HM, Cheng SJ, Yu CH, Chiang CP. Cryogun cryotherapy for oral leukoplakia. *Head Neck.* 2012;34(9):1306-11.
32. Chen HM, Cheng SJ, Lin HP, Yu CH, Wu YC, Chiang CP. Cryogun cryotherapy for oral leukoplakia and adjacent melanosis lesions. *J Oral Pathol Med.* 2015;44(8):607-13.
33. Narula R, Malik B. Role of cryosurgery in the management of benign and premalignant lesions of the maxillofacial region. *Indian J Dent Sci.* 2012;4(2):63-66.
34. Amanat D, Ebrahimi H, Zahedani MZ, Zeini N, Pourshahidi S, Ranjbar Z. Comparing the effects of cryotherapy with nitrous oxide gas versus topical corticosteroids in the treatment of oral lichen planus. *Indian J Dent Res* 2014;25:711-6.
35. Hausamen JE. The basis, technique and indication for cryosurgery in tumours of the oral cavity and face. *J Maxillofac Surg.* 1975;3:41-9.
36. Gage AA. Cryotherapy for oral cancer. *J Amer. reed. Ass.* 1968;204(7):565-569.
37. Murugadoss P, Thulasidoss GP, Andavan G, Kumar RK. Advent and implications of cryosurgery in maxillofacial mucosal lesions. *SRM J Res Dent Sci.* 2016;7(4):242.
38. Gongloff RK. Treatment of intraoral hemangiomas with nitrous oxide cryosurgery. *Oral Surg Oral Med Oral Pathol.* 1983;56:20-4.
39. Bekke JP, Baart JA. Six years' experience with cryosurgery in the oral cavity. *Int J Oral Surg.* 1979;8(4):251-70.
40. Shepherd JP, Dawber RP. The response of keloid scars to cryosurgery. *Plast Reconst Surg.* 1982;70(6):677-82.
41. Mende B. Treatment of keloids by cryotherapy. *J Skin Diseases.* 1987;62(18):1348-51.
42. Zouboulis C, Orfanos CE. Cryosurgical treatment of hypertrophic scars and keloids. *J Dermatol Venereol Allied Fields.* 1990;41(12):683.
43. Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. *Plast Reconst Surg.* 2003;111(6):1841-52.
44. Zouboulis CC, Blume U, Büttner P, Orfanos CE. Outcomes of cryosurgery in keloids and hypertrophic scars: a prospective consecutive trial of case series. *Arch Dermatol.* 1993;129(9):1146-51.
45. Pogrel MA. The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions. *J Oral Maxillofac Surg.* 1993;51(3):269-73.
46. Tonietto L, Borges HO, Martins CA, Silva DN, Sant'Ana Filho M. Enucleation and liquid nitrogen cryotherapy in the treatment of keratocystic odontogenic tumors: a case series. *J Oral Maxillofac Surg.* 2011 Jun 1;69(6):e112-7.
47. Thanabalan D. The use of Cryosurgery in the management of oral lesions. *Int J Sci Res.* 2014, 3(5).
48. Liu J, Yan JF, Deng ZS. Nano-cryosurgery: a basic way to enhance freezing treatment of tumor. *Int Mech Eng Congress Expo.* 2007;42967:87-94.