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Review Article

Cryosurgery- Principles and uses in maxillofacial surgery: A review

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ABSTRACT:
Cryosurgery is a method of causing tissue destruction by rapid freezing in situ. When applied to tissues, it causes direct and indirect changes in the tissues starting from heat transfer and tissue destruction to vascular and inflammatory changes. It is available in open and closed delivery systems which use different cryogens such as nitrous oxide, liquid nitrogen, carbon dioxide, argon or freon. There are various techniques of cryosurgery ranging from use of cotton swabs, thermo-couple devices, forceps technique and use of cryoprobes. Procedure of cryotherapy involves period of freezing followed by a thaw period and this cycle along with cryodose is repeated depending on the size and extent of the lesion. Nowadays it is being widely used in dentistry as well in maxillofacial surgery for treatment of various lesions such as cysts, hemangiomas, lymphomas, mucoceles, several benign and dysplastic lesions of oral cavity, aggressive jaw lesions and even in treatment of neuralgias. It is a simple and effective method with low cost while providing pain free and atraumatic treatment to patients. This review outlines the principles of cryosurgery, its effects on tissues, delivery systems, various techniques and its implications in maxillofacial surgery.

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INTRODUCTION

Cryosurgery is defined as a branch of cryobiology dealing with the therapeutic application of cold at very low temperatures of less than 0°C to destroy tissues in selected target sites.[1] Clinicians have been using extreme cold since centuries for destruction of cells. Robert Boyle credited over 300 years ago that freezing the tissues could be used to destroy the cells. Cryosurgery has been used for treating different types of lesions since that time.[2] Several techniques have been introduced to destroy tissues using freezing.

Application of cryosurgery has been applied in the field of dermatology, otolaryngology, general surgery, ophthalmology and even in oral and maxillofacial surgery for treatment of oral lesions including benign and malignant pathologies such as mucoceles, trigeminal neuralgia, leukoplakia, hemangioma, pyogenic granuloma, human papilloma virus lesions, actinic cheilitis, lichen planus, fibromas, ameloblastomas, myxomas, keratocystic odontogenic tumours, ossifying fibroma, and central giant cell lesions.[3,4] It can be used with special indications in children, adults and elderly. Cryosurgery causes necrosis of the tissues which is allowed to slough spontaneously.[5] It is based on several cryobiologic effects that dependon controlled freezing and thawing.[2]

HISTORY OF CRYOTHERAPY

In 1851, Dr. James Arnott first reported the use of extreme cold solutions therapeutically where he used ice and sodium chloride as a mixture for treatment in tumours. Later in 1920's, liquid oxygen at a temperature of -182.5° C was used as a cryogenic agent. In 1950's, liquid nitrogen was introduced as an alternative to liquid air and oxygen both. At present, liquid carbon dioxide along with liquid nitrogen is the most commonly used cryogen.[5] Earlier, liquid nitrogen was applied using cotton pellets but with refrigeration technology, sprays and probes have come into use now.[6]

PRINCIPLES OF CRYOSURGERY

Several changes take place during the phase of cryosurgery ranging from formation of intracellular or extracellular ice crystals, cellular dehydration, protein denaturation and disruption of cell membranes with some complications resulting in ischemic infarction due to failed microcirculation.[5]

It is said that when a tissue is cooled, there occurs heat exchange that depends on the blood supply, thermal conductivity of the tissues, water content in tissues, rate of freeze as well the temperature of the refrigerant.[6]

The mechanism of cell death is different for different cryogens as they act at different temperatures. For a tissue to undergo cell death, a temperature less than -20°C is required.[5] Cell and tissue death with cryosurgery occurs by the mechanism of intracellular and extracellular ice crystal formation, osmotic and electrolyte disturbances, denaturation of proteins complexed with lipids, and vascular stasis. Vascular stasis is considered to be an indirect effectinvolving arteries andveins, within the ice ball that further lead to cell death and ischemic necrosis of the treated tissue.[2]

Freezing the tissues causes direct as well as indirect effects on the cells and tissues.

Direct effects include rapid heat transfer and tissue destruction.

1. **Rapid Heat Transfer**
   When there is transfer of heat from the tissue to the cryogen, it is called as rapid heat transfer. Transfer of heat is more when the difference of temperature between the cryogen and the tissue ismore resulting in destruction of cells. There is formation of a slowexpanding ice ball that reaches a constant size after some time.[5]
2. **Tissue Destruction**
   The rapid heat transfer causes formation of ice-crystals in the extra and intracellular compartments of cells. Extracellular icecrystals form an osmotic gradient resulting in loss of water fromwithin the cells leading to an irreversible toxic increase in theintracellular electrolytes that fates the cell towards its death and these crystals even lead to disruption of the cell membrane by mechanical compression. Moreover, extreme changes of temperature cause further enzyme inhibition that effects the cellular metabolism and thus, reducing the cell's ability to recover. When the cryogen is removed from the tissue, the temperature of the tissue starts rising, this process is called thawing. The injury is more if the thawing time is longer.[5]

The **indirect effects** caused by freezing are the vascular and immunological changes.

1. **Vascular effects**
   It is reported in some studies that intracellular damage occurs within a minute of thawing, and although there is complete vascular stasis during freezing, normal blood flow returns by 10 minutes.[7] When cold temperature is applied to the tissues, vasoconstriction occurs with decrease in blood flow and the blood flow ceases with freezing temperature. But there is vasodilation as the tissue thaws resulting in edema and damage to endothelium. Increased capillary wall permeability results in further edema as well as platelet aggregation. Eventually, thrombosis occurs resulting in vascular occlusion which leads to ischaemia. This contributes to tissue necrosis over the following hours.[8]
2. **Inflammatory effects**
   Inflammation is the last response to cryotherapy usually seen in form of edema and erythema[1], vesiculation, exudation and sloughing. Within the first hour, there is tissue swelling and hyperaemia. Gross accumulation of extracellular fluid and basement membrane separation during cryotherapy treatment often results in blister formation. Within a day or so, the epithelial surface breaks down to be covered by a greyish yellow coagulum in case of mucosa or thick eschar on skin. Healing of the tissues occurs by secondary intention, the surface gets re-epithialised within 2-3 weeks interval.[7]

VARIABLES AFFECTING THE EXTENT OF INJURY

During cryotherapy treatment, maximum injury is produced if there is rapid freezing, slow thawing and repetition of the freeze-thaw cycle. Coldest tissue temperaturereached and the length of time the tissue is exposed to this temperature should also be taken into consideration, as all parts of the freeze-thaw cycle contribute to cell death.[8]

RAPID FREEZING

Rapid heat transfer is affected by number of variables, that is larger the difference between the temperature of the cryogen and the tissue, more transfer of heat. Also, the rate of freezing is increased at the tip of the probe, and slower further away. Rapid freezing that is equivalent to 50°C per minute or more, produces the most destructive effects in tissue. The fast rate of cooling allows for the maximum amount of the lethal intracellular ice production.[8]

SLOW THAWING

The thawing period should be kept slow so as to increase the maximal lethal effects. During a slow thawing period, the cells present in the periphery of the frozen tissue take up the increased electrolytes, causing swelling and lysis of the cells. There is increase in recrystallisation that produces larger ice crystals which are lethal as they mechanically disrupt the cell.[8]

REPETITION

All these variables contribute to maximal destruction of cells from cryosurgery. Repetition of these in the freeze-thaw cycle causes more necrosis. Every time the tissue is frozen, the cooling is faster due to an increase in thermal conductivity which results in larger and more mechanically disruptive ice crystals in following each freeze.[8]

DIMENSIONS OF THE CRYOLESION

Estimating the depthof freezing can be difficult and it is dependent on the temperature of the cryoprobe tip, the area of contact with the tip and the duration of contact. Cryogens and delivery systems should be chosen that freeze at temperatures of about -50°C. During freezing period, an ice ball is formed and the volume of this frozen tissue is roughly hemispheric so the depth can be estimated as the same as the lateral spread of freezing and larger the diameter of the probe, larger is the area of ice ball.[8]

DELIVERY SYSTEMS

Most commonly, two techniques are being used for application of the cryogen- the closed system and the open system.

- The closed system that uses cryoprobes.
- The open system that uses liquid nitrogen as a spray or on a cotton swab. Spray systems are being used for widespread lesions. Also, open systems that use cotton swabs are considered unsuitable for use in the oral cavity as they have limited control over the temperature achieved in the tissue. Open system methods are considered unpredictable because of rapid evaporation of the cryogen from the delivery apparatus or surface of the lesion.[8]

  A cryoprobe is a precooled metal instrument that is applied to lesions. The cryoprobe works by conduction of heat transfer. The cryoprobe can measure the tip temperature and the amount of pressure that is being used, thus supporting controlled conditions and freeze deeper into the tissue, influencing the depth and lateral spread of freeze.[6,8]

TECHNIQUES OF CRYOSURGERY

The choice of technique used depends on the type of lesion to be treated. There are a few techniques for the application of cryogen. Table 1.

Table.1 Showing various cryogens used in cryosurgery[9,10]

Name of the cryogen	Boiling point(°C)
Chlorodifluoromethane	-41
Dimethyl ether and propane	-24, -42
Carbon dioxide, solid	-78
Nitrous oxide	-89
Liquid nitrogen	-196
Freon 22	-41
Freon 12	-21.8

°C- degree Celcius

DIPSTICK APPLICATOR METHOD

Liquid nitrogen is the most commonly used cryogen. The method uses dipping of cotton in liquid nitrogen. This cotton applicator is then used over the lesion to be treated. The process is repeated until the desired amount of freezing is obtained. This method does not provide the desired amount of low temperature.[1,9]

CARBON DIOXIDE

Solidified carbon dioxide also called as dry ice is used in the form of a stick, block, or snow and is applied directly on the skin. To obtain a light freeze, acetone can be mixed to the dry ice. This is known as slush therapy.[9]

THERMO-COUPLE DEVICE

For the treatment of malignant lesions, a temperature probe that is coupled to digital thermometer can be used which can measure the temperature upto -75°C.[1] One study compared the efficacy of argon based cryoneedle with liquid nitrogen cryoneedle using a thermo-couple device for the treatment of keloid scars.[11] The clinical studies evaluated both the devices with a higher rate of hypopigmentation and a lower rate of recurrence with the argon gas device as compared to liquid nitrogen device.[11]

CRYOPROBE

The cryoprobe is applied directly against the lesion. It is used mainly for round lesions and for lesions with flat surfaces.[9] Cryoprobe causes a decrease in temperature of tissues based on the Joule-Thomson expansion principle. It states that when a cryogen moves from the high-pressure unit within the cryoprobe into the low-pressure cryoprobe tip, it results in a drop of temperature at the site of tissue contact.[12]

In a study by A. Goss and K. Ito in 2020, the authors used aSpembly MM100nitrous oxide cryoprobe with a DO5probe(Spembly Medical Ltd) for the treatment of trigeminal neuralgia. They used a timed three-minute freeze that was calculated from the time of development of an ice ball on the nerve followed by rewarming of the ice ball for 2 minutes with irrigation using warm saline and further did three-minute cryofreeze with rewarming.[13]

Some modern cryoprobes have been developed fitted with tip temperature monitors that allows time selection and increased control. These monitors help to observe theeffects of the probe at a particular temperature which can be used as a basis for future treatment.[14]

FORCEPS TECHNIQUE

Forceps technique is mainly used in the treatment of skin tags. The forceps are dipped in liquid nitrogen for 10 seconds. Thawing is to be completed after the initial freeze no matter how many cycles of freezing are done. Significant cellular injury is seen to happen during the thaw phase and the cell's survival decreases with the complete thawing.[6]

According to the type and site of lesion, the time for a cryocycle is different.Table 2.

Table.2 Shows the duration of cryo-cycle for different lesions.[8]

TYPE OF LESION	SITE OF LESION	FREEZE-THAW DURATION
VASCULAR	Tongue or deeper sites	45 s F–60 s T
VASCULAR	Any	30 s F–30 s T
PIGMENTED	Attached gingiva	30 s F–30 s T
PIGMENTED	Lip	15 s F–30 s T
FIBROMA/PAPILLOMA	Any	45 s F–45 s T
MUCOCELE	Lip	45 s F–60 s T

F- Freeze, T- Thaw

CLINICAL APPLICATIONS OF CRYOSURGERY

Cryotherapy can be used in head and neck pathology in conditions such as premalignant and malignant lesions, benign oral lesions and also in trigeminal neuralgia.[15]Oral lesions that can be treated with cryotherapy include hyperpigmentation of the gingivalormucosal tissues, hemangiomas of the lip and oral mucosa,mucous retention cysts, lichen planus, papillomas and polyps, oral leukoplakia, and oral cancers[5],odontogenic keratocysts[2] and trigeminal neuralgia.[13]

ODONTOGENIC KERATOCYST

In case of osseous lesions, cryosurgery has an advantage as it kills the cells within the bone and leaves the inorganic osseous framework unharmed. This allows it to remain as a matrix for new bone formation. As enucleation of cystic lesions can result in recurrence and resection of the jaw seems to be an aggressive treatment;in such cases, enucleation with curettage is preferred followed by cryotherapy so that it devitalizes a narrow rim of bone beyond visible margins of the lesion to kill any satellite or daughter cells that might have left behind.[16]

Use of liquid nitrogen after enucleation has been shown to reduce the recurrence rates and the need for resection. Freezing the residual bony cavity results in cell death to a depth of up to 1.5 mm.[17]Rapid freezing of tissues by spraying liquid nitrogen for 1 min causes maximum ice crystal formation followed by a slow thaw of 5 min that causes electrolyte imbalance which is then repeated 2 to 3 times to causemaximum cell death. The defect can be managed immediately by grafting and then tight suturing of the overlying mucosa.[18]

The limitation with cryotherapy procedure is the difficulty that might be encountered while controlling the amount of liquid nitrogen that is being introduced into the cavity. Furthermore, making it difficult to predict the depth of penetration and also resulting in unpredictable post-operative swelling, pain and infection.[18]

HYPERPIGMENTATION OF THE TISSUES

In one study, complete removal of the pigmented lesions was seen after a time interval of about 2-3 years. Freeze cycle was done for about 20-30 seconds with a second treatment course done after one week to completely remove the pigmented lesion.[5]

In one study, 20 patients suffering from gingival hyperpigmentation were treated using liquid nitrogen soaked cotton swabs for 20-30 seconds yielding good results at the end of treatment.[10]

In another case study, patient reported with pigmentation on the lower lip since childhood and also gave a history of gradual increase in its size and the presence of secondary area within past 5 years. Biopsy confirmed the diagnosis of melanotic macules which was then treated with a cryodose of 3 consecutive freeze-thaw cycles of 15 seconds each that resulted in complete resolution and no recurrence even by 2 year interval.[8]

LEUKOPLAKIA

Cryotherapy destroys the required area of the mucosal epithelium that has been altered pathologically by leukoplakia. Due to the limitation of damage to epithelium, there is complete regeneration of epithelial structures that overlie the preserved submucous tissue, moreover scar shrinkageof treated mucosal area and subsequent functional impairment are also prevented.[19]In one study, the authors treated ten patients with leukoplakia using nitrous oxide system where they managed all lesions with1½ min freeze and 3 min thaw. Depending on the size of the lesion, the number of sessions ranged from two to three according to the requirement.[10]

PYOGENIC GRANULOMA

In a study by Narula and Malik, pyogenic granulomas were treated using nitric oxide with a cryoprobe set at a temperature of -70°C. Freeze cycle was carried out for 2 minutes followed by a thaw cycle of 4 minutes.[20]

LICHEN PLANUS

Cryotherapy was believed to be a good treatment option for lichen planus even though it did not completely cure it but acted as a palliative treatment. It was found that cryotherapy with nitrous oxide was as good and effective as steroid application in management of lichen planus.[10]

Narula and Malik treated lichen planus patients with the use of nitrous oxide system. They applied two freeze-thaw cycles to each area with a freezing time of one and half minute followed by a thawing time of 3 minutes. Depending on the size of the lesion, number of sessions were decided.[10]

MUCOCELES

A mucocele is a common lesion mainly occurring on the lips, buccal mucosa, tongue tip, and oral floor in salivary gland diseases. Surgical removal is the often plan of treatment but it causes postoperative bleeding and neuropathy. It has been seen that cryosurgery eliminates mucoceles on the lip or buccal mucosa with minimal discomfort. It has a disadvantage that pathological examination cannot be performed prior to the procedure or later.[21]

HEMANGIOMAS

Cryosurgery in the oral region has been used in the management of hemangiomas.It works by the way that the freezing effect stimulates thromboembolic phenomena in the tissues that generates a tissue slough effect. Cryosurgery increases the rate of apoptosis in the vascular lesions. Temperature of about -30°C to -40°C at the tip of probe is considered effective and a mean freezing time of 40 sec per cycle,followed byapproximately 1 min of thawing. The total number of cycles required depend mainly on the size and location of the lesion.[5]

In a case report by Nogueira et al in 2017, a 65year old female underwent cryotherapy for the management of a hemangiomatous lesion on the left lateral border of tongue. The management comprised of use of liquid nitrogen spray in a single session of two cycles of 1 minute each, with a 2minute interval between cycles. It was noted that immediately after the procedure, the lesion was noted to be whitish in colour that characterized the freezing process, and few minutes later, edema and erythema formation were observed in the treated area caused by thawing.[4]

TRIGEMINAL NEURALGIA

Trigeminal neuralgia also known as tic douloureux or classic trigeminal neuralgia is characterised as an intense, sharp shooting and electric shock-like pain on the face or mouth. The pain may last for few seconds to a minute. The treatment varies from drug therapy to extracranial or intracranial surgical procedures. The surgical procedures include alcohol, phenol or glycerolinjections, peripheral neurectomy of trigeminal nerve branches, rhizotomy, cryotherapy, gamma-knife radiosurgery, balloon compression of the root and microvascular decompression.[22]

In the year 1976 Lloyd et al. described the use of cryotherapy for eliminating pain in peripheral nerves. However, surgical exposure of the nerve is required and damage to the adjacent tissue is more likely to occur if the open liquid nitrogen spray is inaccurately applied.[23]

PradelW et al in 2020 did a study using cryotherapy on trigeminal neuralgia patients. In this study, cryoprobe was applied the same way as needle for a nerve block at infra-orbital or mental foramen by an intraoral approach. The system was cooled down for about 40 seconds and the freezing lasted another 90 seconds. Freezing was repeated after the period of thawing. All the patients experienced a reduction of pain within 5 days and freedom from pain within 10-14 days. Follow up was done between 1-3 years and in all the patients, the regions innervated by the treated nerve became anaesthetic.[23]

Cryotherapy saves the anatomical integrity of the nerve, even though freezingcauses deep neuropraxia. Cryosurgery produces a reliable, prolonged and reversible nerve block with no aggravation of symptoms.[24]

In a study by TodaK(2008), the affected peripheraldivisions of the trigeminal nerve were exposed surgically and were frozen by direct application of a fine cryoprobe.[25] In another study, the nerve was exposed surgicallyunder anaesthesia and a cryoprobe at a temperature of -120 degree celcius was applied directly on to the exposed nerve for a standard 3 cycles of 2-minute freeze and 5-minute thaw. Some studies noticed numbness after the use of cryotherapy as a complication.[25]

In a study conducted by Bansal V,Mowar A, DubeyP and Gupta S(2019), trigeminal neuralgia patients were treated with cryotherapy. In all the cases, nerve was exposed and 3 freezing cycles were given to all nerves. Freezing time varied depending on the nerve thickness. Freezing time was 5 minutes for inferior alveolar nerve and 3minute freeze for supra-orbital, infra orbital and mental nerve. All nerves were given a thawing period of 5 minutes.[26] All the patients got relief from pain in their first visit whereasswelling, pain and trismus were seen in all cases of inferior alveolar nerve who recovered with warm saline rinses and physiotherapy. The authors reported loss of response to fine as well as crude touch in all patients which recovered within 4-6 months.[26]

ADVANTAGES

- Simple and effective.[8]
- Low cost.[8]
- Less disturbance to the patient.[7]
- Tissue destruction can be controlled to an extent.[7]
- Aesthetically pleasing.[7]
- Pain free procedure.[8]
- Can be used as an adjunct therapy in case of malignancies before surgeries.[7]

DISADVANTAGES

- Chances of recurrence.[8]
- Histological examination cannot be performed.[3]
- Cannot be used in patients suffering from cryoglobulinemia, cold intolerance, cold urticaria, cryofibrinogenemia, dysfibrinogenemia, Raynaud's phenomenon.[10]
- Can be used only for surface lesions.
- Difficult determination of depth of destruction.[7]

COMPLICATIONS ASSOCIATED WITH CRYOSURGERY

A number of complications are associated with cryosurgery. The complications can be intraoperative complications, early postoperative complications and late postoperative complications.

Intraoperative complications-

- Inadequate choice of equipment and technique.
- Run-off of cryogen with use of cryosurgical device that sprays liquid nitrogen or fast freezing by pouring liquid nitrogen onto the tissues.[27]

Early post-operative complications-

- Bleeding that is hemorrhage from cryoablation site evident in the first 2-3 hours after surgery.
- Excess of tissue necrosis.
- Edema.[27]

Late post-operative complications-

- Recurrence of the lesions.[27]

  Other complications that can be seen are vesicle formation, facial scarring, Wallerian degeneration, alopecia or ectropion.[20]

CONCLUSION

Cryotherapy is considered safe, effective and a promising modality for resolution of many benign and malignant lesions. It is believed to be a atraumatic treatment compared to many surgical procedures. It may be convenient for those patients who are afraid of surgical procedures or in infants, elderly and immunocompromised patients. With different cryogens and devices available, cryosurgery has come up with excellent results with number of freeze-thaw cycles taken into consideration. Cryotherapy has been shown to have a very high success rate with very minimal incidence of postoperative complications.

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