Cryotherapy: An Alternative to Surgical Adjunct

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Abstract

The application of low controlled temperatures had advanced in recent years in many branches of surgery. Cryotherapy has opted as an option to destroy cancerous cells in mostly the head and neck region. In many cutaneous conditions, it has been productively used. It is a therapeutical process in which tissue inflammatory and destructive response is done by freezing. Hence, it deliberately destroys tissue by using severe cold. Mouth is reasonably accessible due to oral mucosa's moist surface that is well suitable for the application of cryoprobe. We will discuss how cryotherapy can be used instead of surgical procedures.

Keywords: *Cryotherapy; Applications; Surgical Procedures.*

Introduction

From generation to generation, many different techniques are used for tissue destruction other than the surgeon's knife, some of which can be summed up as high-frequency electric current, chemicals, irradiation by X-rays. And the advantages that are being looked upon them instead of using scalpel are painless and cause minimum destruction of surrounding tissues, and encourage speedy and uneventful healing. In 1845, James Arnott reported the use of low temperature to destroy cancerous cells and came the term Cryotherapy. It is derived from a Greek word 'Kryos' which means frost, thus meaning frost therapy.[2]

According to the medical definition, it is defined as a procedure used to destroy the tissue of both benign and malignant lesions by the freezing and re-thawing process. It is done with the use of cold, which is applied locally or generally various methodto lower the temperature of tissue that is affected.[3] Over 30 years, it has been used in Oral Medicine and Pathology as the oral lesions are normally warm and moist, therefore the procedure is preferably suited for treatment. A cryoprobe is used to attack the oral lesion constantly, which requires minimal preparation of the patient and operation field. It is considered as a simple procedure.[4]

Earlier it was used for the treatment of cancer of oral cavity and lip, but now as the technology has expanded and advanced in the head and neck region. This procedure is also advised after numerous surgical procedures.[4]

The different cryogens used in the procedure are:[6]

1. Liquid nitrogen (-196ºC)
2. Nitrous oxide (-89ºC)
3. Solidified CO2 (-78ºC)
4. Chlorodifluoromethane (-41ºC)
5. Dimethyl ether (-24ºC), Propane (-42ºC)(1)

The combination of these cryogens had also been proved to be used for the treatment of jaw lesions, and had shown a therapeutic effect.[7] In this process the tissue is not excised, rather the lesion is frozen and the ensuing necrotic tissue is allowed to slough instinctively. The main mechanism of the destruction of tissue is through intra and extra-cellular ice crystal formation, leading to cell dehydration, protein denaturation and disruption of the cell membrane and ultimately death of the cell, irrespective of the cryogen used or its temperature.[8] All biological tissues subjected to a temperature of -20ºC or below does undergo necrosis for a minute or more virtually.[9] In cryotherapy, the tissue which is close to the probe freezes quickly, but ice, in this case, acts as an insulator so the further freezing continues slowly. As the spread of freezing is delayed with the help of ice, the probability of unintentional damage to the underlying tissue is reduced. The neighboring tissues are unharmed due to the gradient of heat loss.[10]

The basic attitude of the procedure is: Rapid cooling -> slow thawing -> freezing process is done repeatedly -> maximize tissue destruction. The two method used for the process are:

a. Use of probes and nitrous oxide in a closed system.

b. Use of nitrogen and cotton tip in an open system.

According to Joule Thompson expansion, a substance undergoes a drop in temperature when moved from a high-pressure area to low pressure area. This principle is followed by the probe in cryotherapy, for example when from high pressure inside the cryoprobe nitrous oxide is released to the cryotip which is low in pressure, there is a drop in temperature which causes freezing of tissues to happen.[1,7,11]

History[2]:

1. Theuse of cold for inflammation and trauma was first done by the Egyptians.
2. In the 17th century- Robert Boyle bring into beingthat by freezing cells would be killed.
3. In the 19th century- In cryosurgery, the use of nitrogen and nitrous oxide was started.
4. In the 20th century- Baron Lorreyobserved its efficacy in sedation and anesthesia in the amputation of soldiers.
5. In 1845- The first report on the therapeutic use of low down temperatures in malignant diseaseutilizing salt/ice mixture applied to breast neoplasms was by James Arnott.
6. In 1877- Louis Callitet and Raul Pictetoffered liquefaction of oxygen and carbon monoxide experimental papers, and this was considered by Zacharian as the birth of modern cryogenics.
7. In 1899- The first cryosurgeon to use it for medical purposes was Campbell White.
8. In 1977- After freezing there was local tissue necrosis and vascular stasis, and that excellent healing of tissues was witnessed by John Hunter.
9. In the early 1960s- Amaral et al. made use of liquid nitrogen on swabs to treat cases of palatal inflammatory papillary hyperplasia.
10. In 1981- Mac Donald et al. suggested for treatingangiomas, hyperplasia of palate, leukoplakia and lichen planus, cryosurgery can be done.
11. In 1981- Barnard illustrated that cryotherapy produces an extended and reversible nerve block in the management of chronic pain and postoperative pain.
12. In 1988- Goss made use of cryoneurotomy for treating patients with intractable neuralgic pain in the preauricular region.

Role of Cryotherapy in Oral Lesions: It has shown tremendous effects in treating oral lesions in all these years with its rapid and uneventful healing. Patients have been seen accepting the treatment as it is less painful and damage to surrounding tissues is very less. The oral precancerous lesions are treated and eradicated with different other modalities like surgical excision, photodynamic therapy, laser surgery and many more, but the different advantages that make cryotherapy as an effective and alternative modality for treatment are very low incidence of secondary infections, lack of scarring and pain and most importantly bloodless treatment. The different oral lesions in which cryotherapy as a mode of treatment can be used are hyperplastic, keratotic, vascular, granulomatous pigmented lesions, and also lesions of gingiva and salivary glands. As given by Hocut et al in 1982, the different stages of cryotherapy are:[12]

Stage 1: sensation of cold 1-3 min.

Stage 2: aching or burning 2-7 min

Stage 3: local numbness 5-12 min

Stage 4: deep dilation >12 min

It has been suggested that after an injury >12 min should be used to attain stage 3.

The dependency of cryolesion dimensions is based upon three variables, which are:

a. Temperature of cryotip

b. The period of contact

c. Area of contact between the tip and the tissue

The determination of the velocity of freezing within the cells and the size of the freezing ball is a contribution by the temperature of the cryotip. A high velocity of freezing desired since rapid freezing can cause lethal effects to the tissues. The duration of freezing is directly proportional to the size of the lesion in the starting 1-7 minutes, according to the growth pattern of cryolesion

in vitro.[1,6] Taking an example of freezing a bony tissue, in that case multiple freeze sites are necessitated as the freezing of tissues is a difficult job. But in most of the soft oral lesions, the freezing time is limited to 20-30 seconds.

Mechanism of tissue damage in Cryotherapy: It has been determined with the help of several reports that most tissues freeze at a temperature of -2.2ºC, and for cell death to occur the temperature must fall below -20ºC. According to dermatological guidelines, it was suggested that small cancers should be treated at a temperature of 30ºC which is said to be effective. On the other hand, in aggressive cancers of the oral cavity, the treatment is done by repetitive freeze cycles of at least -50ºC or more temperature for the necrosis of tissue to occur.[1,6,10] Normally following the treatment, cryolesions are impossible to differentiate from original tissue, though as repetitive freeze and thaw cycles are undergone by the lesion, an accretion of damage takes place. And in the following days of the treatment, latent damage is created, which changes to progressive damage leading to consequent tissue necrosis.[7] Therefore, after cryotherapy tissue destruction is a multifactorial process, which combines both direct and indirect effects.[2]

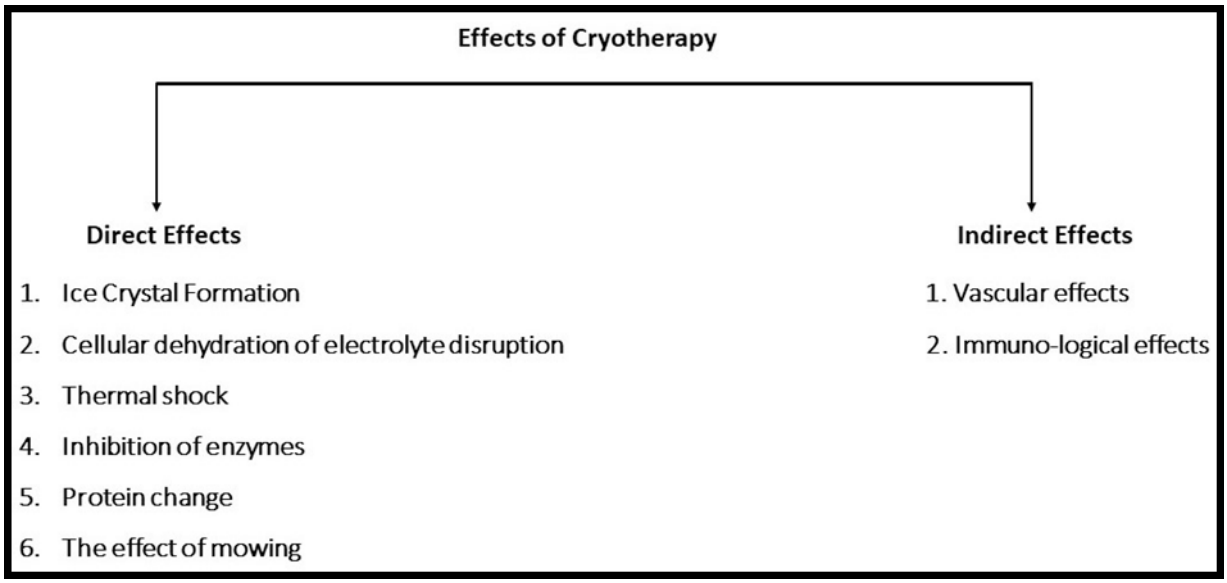

Figure 1. Effects of Cryotherapy

The description of the effects is given the following:

1. Direct effects

a. Ice crystal formation: Larger ice crystals are formed when the cooling rate is more rapid, therefore the degree of adhesion of the tissues to the probe is greater. The disruption of cell membranes is produced due to large ice crystals.

b. Cellular dehydration and electrolyte disruption: The cell membrane acts as a barrier to the propagation of ice crystals as the freezing occurs only in the extracellular space only within the outer zone. The extracellular molecules are captured by the slowed-down freezing, so in the extracellular space the ionic concentration of electrolytes is increased. Intracellular water is passed from the cell, but is then trapped in the ice front, leading to the cells to become dehydrated and undergo physical shrinkage. And the concentration of electrolytes both inside and outside of the cell is amplified, which becomes irrevocably toxic to cellular function.

c. Thermal shock: This is related to the rapid freezing rate which causes cell damage, systems recording temperature in order of 1000ºC/minute.

d. Inhibition of enzymes: Sudden cooling acts as an inhibitor, as each cellular enzyme operates optimally over a narrow temperature range. This makes the cell more susceptible to metabolic changes.

e. Protein changes: Protein is denatured in both the

cell membrane and mitochondria due to the fall in temperature, and cellular metabolism shows subsequent damage.

f. **The effects of thawing:** The tissues are allowed to re-warm when the process of freezing stops which causes damaging effects. Like, due to increased concentrations of intracellular electrolyte, the cells show water intake which is then vacuolated, bulged and burst.[13]

2. Indirect Effects:

a. Vascular effects: Vascular stasis and microthrombus formation causes ischaemic necrosis, which plays a significant role in cryodestructive process.[14]

b. Immunological effects: These effects could be seen due to the massive release of pathological cell antigens, which makes them vulnerable to host surveillance mechanisms. These also add to the damage of affected tissues treated by cryosurgery.[2]

Changes of tissue after cryotherapy: The clinical observations done in oral soft tissue include necrosis, sub epithelial hemorrhage, tissue edema, blister formation, sloughing and repair. In general cases, within a few hours of cryotherapy, edema, hyperemia or erythema is seen immediately. After 1-2 days, local swelling is seen which increases with time, followed by superficial necrosis and ulceration that is enclosed by a coating of yellowish or whitish necrotic pseudomembrane. After the 1st week, this yellowish or whitish slough is detached from the underlying tissue, leaving a granulating clean surface that is covered by epithelium partially. After 1-4 weeks, the completion of epithelialization is witnessed with no or very small scar formation.[6,9]

Cold therapy after intraoral surgical procedure: It has been observed that patients are always advised to apply ice after physical injuries and a variety of surgical procedures for therapeutic use. This therapeutic use of cold through various method is applied locally or generally to lower the temperature of the skin and subcutaneous tissue.[12,15] Many scientific studies are being done based on the physiological and clinical effects of cryotherapy but still there is a scarcity of information based on what should be the optimal time interval for therapy, the finest method of application and the entire time length for cryotherapy.

The five cardinal signs of inflammation pain, swelling, heat, redness and loss of function were identified long ago, but they are not the inflammatory response. The overlapping stages that can impair tissue function or structure are referred to as inflammatory response. The physical objectives that can be obtained when cold therapy is applied after an injury to cool tissues are edema (inhibit swelling), decrease inflammation, vasoconstriction (diminish blood supply), stopped the increase of temperature, reduced hemorrhage, decreased metabolic alterations leading to reduction of secondary infection due to lack of oxygen, cold reduces nerve conduction speed and eventually hurry up the revival process of the patient to resume normal function.[16]

Advantages: Cryotherapy is the most effective and best method of treatment when surgery is contraindicated in the patient. It causes very minimal general disturbance to the patient, especially the elderly age group. The volume of tissue destruction is reasonable and predictable. It is best suited for extensive superficial lesions, with a very low complication rate. It can be used as an adjunct to surgery and also radiotherapy in case of analgesic tumor control. It also helps in the preservation of the inorganic structure of bone, with minimal to no visible scarring. It also has a very low incidence of secondary infection. It is said to be safe, easy to perform, with no permanent side effects and more localized in action. It is a relatively inexpensive technique in an outpatient clinic for various oral lesions.[7,10,12,17]

Drawbacks: The technique is very safe and useful in treating oral lesions, but has got a few limitations also. Like, it is highly dependent on the operator skill and experience. The freezing capacity of the available instrument doesn't always reach the volume of the lesion which leads to multiple cryosurgery procedures or an alternative mode of treatment that has to be planned. Sometimes there is trouble in evaluating the extent of the lesion, which leads to an insufficient amount of tissue involvement which results in persistence of the pathologically changed epithelium and recurrence of the lesion. The healing process is slow in cryotherapy, which can also mean the persistence of lesion, especially if the case is neoplastic. Extensive procedures can lead to considerable scarring. It is contraindicated in patients with cold intolerance, cryoglobulinemia, cold urticaria, collagen diseases, and patients undergoing hemodialysis or immunosuppressive therapy.[3,7,18-21]

Conclusion

In comparison to conventional surgical procedures, it is an atraumatic form of therapy. Therefore it can be the choice of treatment in case of anxious patients, children,

and patients for whom surgery or other procedure is contraindicated. It is an effective mode of treatment for the head and neck region. By careful selection of patients, cryotherapy is a simple, safe, conservative and acceptable treatment for certain benign oral lesions and oral pre-cancers. The ice therapy canprovide several benefits that can be said after a lot of reviews on the physiological effects of the cold application, still many clinical trials are required to prove the therapeutic efficiency of cryotherapy.

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