

Cryotherapy – A Review

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ABSTRACT

Cryotherapy is a unique therapeutic modality which uses cryogens for destruction of tissue.

Keywords: Cryogens, Thawing, Warts, Hypertrophic scars, Keloid.

INTRODUCTION

James Arnott (1797-1883) was the first person to use extreme cold locally for the destruction of tissue, Hence called the father of modern cryosurgery. He used a mixture of salt and crushed ice 'two parts @ nely pounded ice and one part of chloride of sodium¹ for palliation of tumours, with resultant reduction of pain and local haemorrhage. He stated that a very low temperature will arrest every inflammation which is near enough to the surface to be accessible to its influence

He designed his own equipment, consisting of a waterproof cushion applied to the skin, two long flexible tubes to convey water to and from the affected part and a reservoir for the ice/water mixture and a sump.

He exhibited this at the Great Exhibition of London in 1851 and won a prize medal for his effort². Torre developed a liquid nitrogen spray in 1965 and Zacarian a hand-held device, the Kryospray, in 1967²⁰

Zacarian popularized the use of this equipment. Zacarian's spray allowed one-handed operation with trigger type control, and interchangeable tips permitted variations in spray diameter. Zacarian also developed copper probes that allowed tissue-freezing to depths of up to 7 mm.

Amoils developed a liquid nitrogen probe that achieved cooling by expansion. He performed cataract extraction (cryoextraction) successfully but cooling was slow and temperatures were not low enough for tumour work. This system is still widely used in gynaecology and ophthalmology. Rand performed a transphenoidal hypophysectomy with liquid nitrogen, Gage treated oral cancers and Cahan performed cryosurgery of the uterus with a liquid nitrogen probe.

For malignant lesions freezing times are longer than for benign lesions since destruction of all malignant cells is vital. Tissue temperatures

must be below -75°C for adequate treatment of tumours. A 30-second spot freeze, counted 30 seconds after an iceball formation, is capable of achieving a tissue temperature of -75°C in the centre of the ice ball and is usually the minimum time necessary for tumour work³.

Melanocytes are most sensitive, hence the depigmentation of skin often seen after cutaneous cryosurgery. Collagen is the most resilient tissue, and indeed preservation of the normal structure of collagen bundles is observed on electron microscopy even after the deep freezes necessary for tumour work. This explains why there is so little scarring.

Cartilage necrosis is extremely rare, so cryosurgery is particularly suitable in areas where maintenance of elasticity and function are important such as the ear, around the eyes and the nose.

MECHANISM OF ACTION OF CRYOTHERAPY

1. Freezing of tissue: causes Intracellular ice formation – damages cell organelle. Extracellular ice formation – damages cell membrane.
2. Osmolarity increases in extracellular compartment as a result of increased concentration of electrolytes as a result of water withdrawal during ice crystal formation causing disruption of cell membrane.
3. Local ischemia occurs due to vascular spasm and freezing of feeding vessels with resulting necrosis of tissue and small microthrombi formation.
4. Thermal shock – a term used to denote a precipitous fall in the temperature of living cells to subnormal temperatures above 0°C
5. Denaturation of Lipoprotein complexes within the cell membrane.

6. Immunologic (applicable to warts)
Local-Destruction of affected cells and stimulation of immune system and generation of long term memory cells.

Systemic- Destruction of Distant affected cells by the circulating stimulated Lymphocytes.

CHARACTERISTICS OF CRYOGENS

CRYOGENS	EFFECTIVE TEMPERATURE	MODE OF APPLICATION
Ethyl chloride	+13.1°C	Spray
Salt ice	-20°C	Gauze
CO ₂ Slush	-20°C	Gauze
Fluorocarbons Frigiderm (Dichlorotetrafluoroethane)	+3.6°C	Applicator, Probe, Spray Spray
Freon 22	-30°C	
Freon 12	-41°C	
CO ₂ Snow	-79°C	Gauze, Spray (gaseous CO ₂)
Liquid Nitrous oxide	-89°C	Probe
Helium	-185°C	
Liquid Nitrogen	-20°C	Swab
	-196°C	Spray, Intralesional

METHODS OF CRYOSURGERY

CRYO-SLUSH

Cryogen used for cryoslush is solid CO₂ (-20°C). Solid CO₂ is mixed with acetone-when added to dry ice, it lowers its temperature. It also prevents CO₂ from sticking to the skin and thus protects from superficial burns and allows free movement of the gauze ball over skin.

2) sulphur-comedolytic.

Indications: Acne scars, wrinkles, acne grade III-IV.

Endpoint: crackling sound, White frost formation.

CRYOSLUSH



DIPSTICK METHOD

Cryogen used is Liquid nitrogen. Cotton tipped applicator is dipped in the cryogen and is then

applied firmly to lesion till a narrow halo of white ice forms around the bud.

DISADVANTAGES

- 1) Dribbling from the stick can lead to superficial burns.
- 2) Cannot achieve < 20°C beyond 2-3mm depth.
- 3) Slow freeze spread.
- 4) Viral contamination may occur.

CRYOSPRAY METHOD

OPEN METHOD

Method of application: Fill the cryojet unit with liquid nitrogen till 2 inches from the brim. Wait for 3-4 mins to pressure to build up. Select the appropriate cryoprobe. Mark the periphery of the lesion and spray at the centre of the lesion from a distance of 1 cm. Confirm the complete melting of ice ball before starting 2nd freeze-thaw cycle.

CRYOSPRAY



SPRAY TECHNIQUE

1. **Spot** –Here spraying is done over the centre of lesions < 2 cm, -40 °C to -60°C attained till 5-6mm. If the lesions

are > 2cm, then the total area is divided into overlapping circles of 2 cm diameter and treated separately.

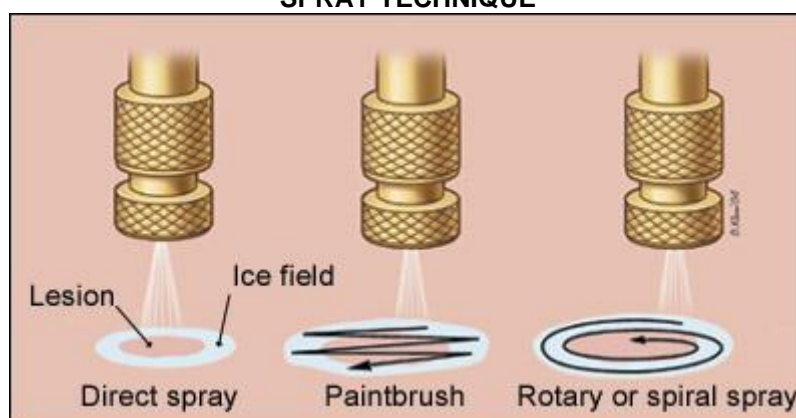
2. **Paint brush:** this technique is employed for large irregular lesions. Spraying is done as in painting moving vertically with simultaneous forward progression.
3. **Spiral:** employed for larger lesion where spraying is started in the centre

of the lesion and gradually moving out to the periphery in a spiral fashion.

4. **Rotary:** In large lesions, spraying is done along concentric circular pathways with gradually increasing diameter moving from inside to outside.

Advantage: This is a 'No-touch' technique and hence ideal for treating HIV/HBV/HCV affected Patients.

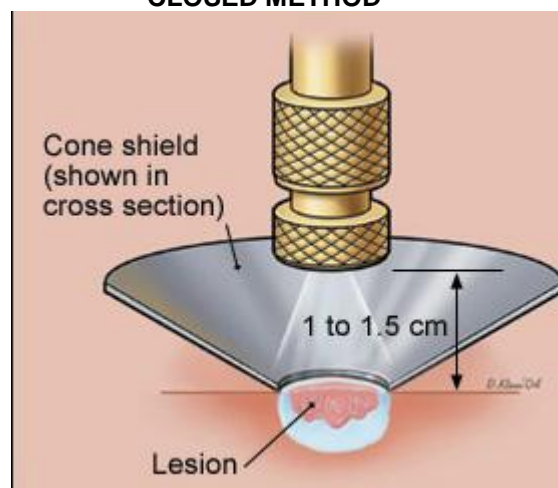
SPRAY TECHNIQUE



CLOSED METHOD

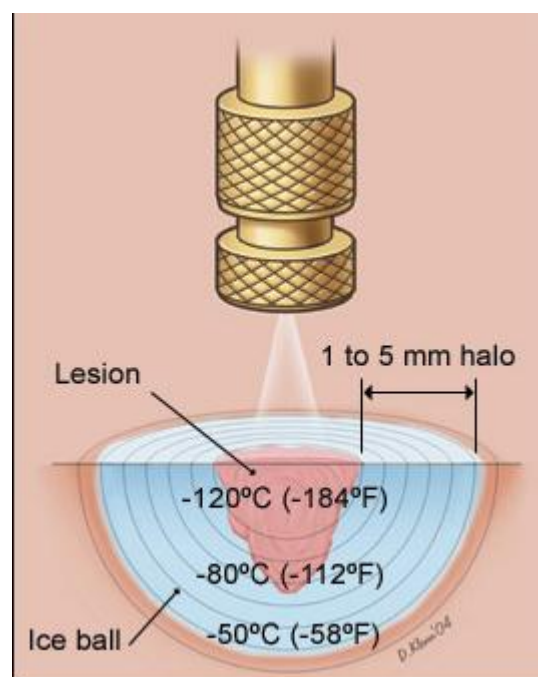
Method of application :Here cones and cylinders (Plastic, Metallic) are used to restrict the lateral spread of the spray and hence should be used when working adjacent to eyes.

CLOSED METHOD



ADVANTAGES

1. Prevents Lateral Spread.
2. Concentrates the Freeze.
3. Achieves rapid fall in temperature.



CRYOPROBE

Method of Application: The tip of the probe is cooled by circulating liquid nitrogen and the probe is placed over the lesion to be treated. The size of the probe selected must be $\frac{3}{4}$ th of the lesion size. Probe should be removed after sufficient thawing. The main advantage is

that pressure can be applied and hence greater depth of freeze can be achieved. The main disadvantage is that slower rate of freeze.

CRYOPROBE



CRYOROLLER

Here the metallic roller made of stainless steel or brass is dipped in liquid nitrogen and is rapidly rolled over the treatment area. The main indications are Acne scars, Hypertrophic scars and Keloid.

CRYOROLLER



FORCEPS TECHNIQUE

The forceps is dipped in cryogen and then the pedicle of the pedunculated lesion is compressed with its tip. The main indication of Forceps technique is for Pedunculated lesions. The main advantage of this technique is that it acts both mechanically by crushing the lesion as well as by cold cauterization due to cryotherapy.

INTRALESIONAL CRYOTHERAPY

Method of application: Long metallic luer lock spinal needles passed through and through the deeper part of lesion. Cryogen (Liquid Nitrogen) is passed through this needle.

This technique is employed for thick lesions, as other modalities are ineffective below 2 cm depth like keloids. The main advantage is that it spares the surface epidermis and hence lesser chance of depigmentation. The main disadvantage is that it causes necrosis of overlying tissue.

Lesion	Technique	Freeze time(seconds)	Number of FTC,s	Margin	Number of Treatment sessions	Interval (weeks)
Warts	OS	10	1	2	3	4
Hypertrophic scars	OS/P	20	1	2	1	
Keloid	OS/P	20-30	1	2	3	8
Skin tags	F/OS	5	1	2	1	

OS= Open spray

P= Cryoprobe

F= Forceps

FTC = Freeze Thaw Cycle. Total duration of Freezing followed by thawing.

Freeze time = It is the duration of freezing measured after the formation of ice ball.

Thaw time = It is the time required for restoration of normal skin temperature in the lesional area after the cessation of freezing. It is approximately twice the freeze time.

USES OF CRYOTHERAPY

In the treatment of Parkinsons disease and other movement disorders by freezing thalamus

Treatment of Retinal tears, Glaucoma, Eyelash ablation in Trichiasis, Treatment of retinopathy of prematurity and retinal detachment.

1) Cryocauterization

Benign Lesions

i) Infective- Warts, Molluscum

Warts are intraepidermal tumors of the skin and mucosa caused by infection with the Human Papilloma Virus (HPV). Cryosurgery with liquid nitrogen will remove the lesion and usually leave no scar and little or no pigmentary change. Nonblistering therapy (10-20 second application) every 2-3 weeks until resolution is generally effective. This treatment destroys not only the virus but the cells within and surrounding the lesion that contain HPV. Combination therapy with liquid nitrogen cryosurgery and keratinolytic therapy with salicylic acid are more efficacious in treating resistant warts. (Caballero Martinez F et al 1996). Liquid Nitrogen cryosurgery is excellent for condyloma acuminatum. Application should be repeated every 3 weeks until the lesions clear.

Molluscum contagiosum is a viral tumor caused by DNA containing Pox virus. Cryotherapy with liquid nitrogen by spray or Q tip application (5 to 10 seconds) or dry ice is generally the best treatment. Treatment can be repeated in 2 to 3 weeks intervals as needed. After this treatment patient experiences Hyper or Hypopigmentation or scarring. (Valentine CL et al 2000)⁹

ii) Non-infective – Keloid, Hypertrophic scars, Pyogenic granuloma, Skin tags, Seborrheic keratosis, mucous and myxoid cyst, angioma.

Keloids and Hypertrophic scars represent an excessive and aberrant healing response to cutaneous injuries such as acne, trauma, surgery and piercing. Common anatomical sites for keloids or hypertrophic scars are earlobes, chest, lower legs and upper back. Hypertrophic scars remain in the area and shape of original injury and resolve spontaneously or with treatment usually within several months whereas keloids expands beyond the site of initial trauma and are recalcitrant to treatment.

Cryotherapy causes ischaemia that leads to subsequent necrosis and flattening of

tissue. Keloids are treated with two to three freeze thaw cycles of 30 seconds each. Local anaesthesia may be necessary. Complications include pain, edema, hypoaesthesia and hypopigmentation. Cryosurgery is less favourable treatment option for patients with dark skin colour. (Zouboulis CC et al 1993)¹⁰

Skin tags (acrochordons) are small papillomas found commonly on the sides of the neck, axillae, upper trunk and eyelids of middle aged and elderly people. Obesity, Pregnancy, menopause, endocrine disorders like acromegaly predispose to these benign epithelial hyperplastic lesions. For treating the skin tags, the base of which is grasped with a forceps and direct liquid nitrogen spray at the lesion until frozen. The use of the forceps helps to prevent transmission of the cryogen to the skin minimizing the chance of hyper or hypo-pigmentation and allows a deeper freeze of the individual lesion. Alternatively, dip the tip of a Hemostat, forceps or needle holder into a Styrofoam cup with liquid nitrogen for 15 seconds without allowing the hinge to freeze. Use this instrument to grasp the lesion for 10 seconds. (Good Heart 2003)⁸

Premalignant lesions- Leukoplakia, Bowen's disease, actinic keratosis, Erythroplakia of Queyrat.

Malignant Lesions- BCC (except Morpheiform), SCC, Lentigo Malignant Melanoma, Palliative therapy for inoperable carcinomas.

Basal cell carcinoma arise from pluripotent cell in the basal layer of epidermis or appendages. These tumors tends to grow very slowly, over months to years, with an extremely low rate of metastases (< 0.025%).

For Basal cell carcinoma Liquid Nitrogen cryotherapy by spray technique is preferred. Local anesthesia should be obtained and then two cycles of a 30-second full freeze and a thaw of at least 90 seconds should be performed. The site will swell, become painful and blister over 1-2 days. The subsequent lesion takes 2-6 weeks to heal and will leave a hypopigmented, slightly sclerotic scar. Side effects of this treatment may include alopecia, Permanent hypopigmentation and nerve paralysis. For tumors < 2 cm, the recurrence rate is 2-6%.

2) Superficial Acne scars – cryo roller (Liquid Nitrogen).

- 3) Inflammatory acne- Cryo slush(solid carbondioxide),cryo-roller(liquid nitrogen).
- 4) To soften keloid and decrease pain during intralesional steroid injection.
- 5) Non surgical facial rejuvenation.
- 6) For cooling the skin surface during laser therapy for hair reduction and telangiectasis and hence protect the epidermis from heat damage.
- 7) Increases Laser fluence and Irradiance.
- 8) Frozen sectioning of skin biopsy for rapid diagnosis of staphylococcus scalded skin syndrome.
- 9) Cryopreservation of fragile vesicle during biopsy (ethyl chloride).
- 10) As a topical anesthetic (ethylchloride).
- 11) Freezing of cutaneous myiasis (chronic migratory type) and extraction of the larva.
- 12) Mohs Microsurgery is an excisional surgical technique in which horizontally oriented frozen sections are evaluated on the lateral and inferior borders of the tumour to determine where residual tumour is present. This has the advantage of sparing tissue and providing a high cure rate for difficult or recurrent tumors.

Indications of Mohs surgery are immunosuppression, location ears, eyelids, lips, nose, temples, hands, feet, genitalia, aggressive pathology (morpheaform, micronodular, infiltrative, tumors > 2cm, those occurring on embryonic fusion planes (pre and post auricular crease, nasofacial sulcus, nasolabial folds), recurrent tumors, poorly defined tumors or tumors arising in scars or sites of previous radiation. (Swanson NA 1983)¹¹

- 13) Treatment of uterine fibroids and Cervical neoplasia.

CONTRAINDICATIONS

- 1) Cold aggravated /precipitated conditions, viz cold intolerance, Raynauds Phenomenon, Cryoglobulinemia, Urticaria.
- 2) Undiagnosed Lesion.
- 3) Multiple Myeloma, Agammaglobulinemia, CTD.
- 4) Atherosclerosis.
- 5) Concurrent Immunosuppressives.

COMPLICATIONS OF CRYOTHERAPY

Acute: Pain, Headache, oedema, Blister formation, syncope, fever.

Chronic: Hypo/Depigmentation, Hyperpigmentation, milia, hypertrophic scar/keloid, arthralgia, nerve damage, paraesthesia, atrophy, cicatricial alopecia, ectropion, notching of eyelid, necrosis of cartilage.

Others: Infection, Hypertrophic Granulation.

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