Principles of Cryotherapy

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Contents

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8.1 Introduction

Cryotherapy (or cryosurgery) is the technique of precise freezing and thawing of undesirable tissue resulting in cell death and regression. It is a highly effective technique available to the ophthalmologist for local control and eradication of various intra- and periocular tumors and can serve as an alternative or adjunct to other methods such as surgery or radiotherapy.

Arnott described crushed ice and salt (NaCl) used to freeze advanced breast and uterine malignancies in the mid-nineteenth century [1]. By the beginning of the twentieth century, solid CO_2 was being used to treat various skin and gynecologic cancers [1]. During this period, most freezing devices were crude and were only able to penetrate superficial layers of tissue, which limited its clinical application.

The commercial availability of liquid nitrogen and the introduction of the cryoprobe by Cooper and Lee in the 1960s heralded significant advancements in the field [1, 2]. For the ophthalmologist, modification of the cryoprobe led to significant surgical advances in cataract extraction, glaucoma management, and repair of retinal tears. Subsequent pioneering work by Lincoff [3], Fraunfelder [4], and Jackobeic [5] led to application of cryotherapy in the management of various intra- and periocular tumors.

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8.2 Mechanism of Tissue Injury

Initially, the cryoprobe begins cooling the tissues with removal of heat. Over time, tissue in contact with the probe freezes. Subsequently, the freezing interface progresses in an outward direction resulting in a temperature distribution that is coldest at the point of contact with the probe. Once freezing is complete, thawing is facilitated by heat from the adjacent tissues [1, 6].

8.2.1 Direct Effects

Microscopically, the initial decline in temperature in the extracellular space forms crystals, leading to a hyperosmotic environment, extracting water from the cells, and causing them to shrink. As the temperature lowers, intracellular crystals form, leading to disruption of organelles and cell membranes. This affects the ability of membrane proteins to control intracellular ionic content. During the thawing phase, as the frozen water crystals dissolve, the extracellular space becomes hypotonic. Limited only by a defective cell membrane, extracellular water enters the cell and disrupts it [7]. In addition, the cold temperature physically disrupts the cellular cytoskeleton and denatures proteins [1, 6].

8.2.2 Indirect Effects

Freezing temperatures are also associated with vascular stasis and cellular anoxia. Initially, the cold temperatures lead to vasoconstriction followed by vasodilation, increased vascular permeability, and edema during the thawing process. Endothelial damage leads to stagnation of blood and thrombus formation. The resultant hypoxia promotes tissue necrosis. Some experiments suggest that this mechanism is more important in the death of tumor cells than direct injury from freezing.

8.3 Technical Aspects

Certain technical factors such as tissue temperature, cooling rate, freeze-thaw cycle, and the number of repetitions influence the efficacy of cryotherapy [8, 9].

8.3.1 Tissue Temperature

Tissue temperature is the most important factor with cell death occurring at temperatures between −20 and −50 °C [10].

8.3.2 Cooling Rate

A rapid cooling rate is more effective in causing cell death.

8.3.3 Freeze-Thaw Cycle

Studies indicate that a slow thaw is among the most important variables contributing to cell death.

8.3.4 Number of Repetitions

Multiple freeze-thaw cycles further increase cell damage and death [11].

8.4 Indications

Over the past 40 years, the indications for cryotherapy have expanded to a number of intra- and periocular tumors. In some instances, it serves as

primary treatment, while in others it functions in an adjuvant setting.

8.4.1 Eyelid Tumors

Eyelid lesions including actinic and seborrheic keratosis are generally amenable to cryotherapy sometimes combined with surgical excision. Basal cell carcinoma particularly lesions less than 1 cm in diameter can be cured with this approach. Select cases of squamous cell and meibomian gland carcinoma of the lid have also been treated with cryotherapy as an alternative to surgery and/or radiotherapy [12–15].

8.4.2 Conjunctival Tumors

In the adjuvant setting, cryotherapy plays an important role in the management of conjunctival lesions. Conjunctival intraepithelial neoplasia and squamous cell carcinoma [16], conjunctival melanoma, and primary acquired melanosis with atypia [5] are amenable to adjuvant cryotherapy [17]. It has also been described in the management of large bulky lesions where complete excision was challenging including papillomas and lymphomas [18].

8.4.3 Intraocular Tumors

Certain intraocular tumors (particularly those anterior to the equator) are amenable to cryotherapy as the treatment of choice. Small peripheral retinal capillary hemangiomas [19], Coats's disease, and retinoblastoma foci (those less than 2 mm in thickness) respond well to cryotherapy [20].

8.4.4 Orbital Tumors

The cryoprobe can be used intraoperatively to assist in the excision of orbital lesions such as cavernous hemangiomas and dermoid cysts. The probe is applied directly to the lesion allowing for traction and careful dissection from adjacent structures. The technique of freezing uveal melanoma, prior to transection of the optic nerve ("no touch" enucleation) is currently used infrequently [21, 22].

8.5 Techniques of Cryotherapy

Cryotherapy can be applied in various fashions depending upon the indication and location of the tumor.

8.5.1 Eyelid Tumors

Eyelid tumors can be treated with a liquid nitrogen spray. Following local anesthesia, the area is draped and an ocular protector is placed over the eye to prevent freezing of the globe or adjacent structures. A thermocouple is inserted into the center of the lesion to monitor its temperature (recommended target temperature −50 °C). Freezing is applied to the lesion and a margin of adjacent normal appearing skin. A double freeze cycle is usually administered.

8.5.2 Conjunctival Tumors

Conjunctival tumors are generally treated with a hammerhead-shaped cryoprobe. In most instances, cryotherapy is performed as an adjunct to surgical excision. Following removal of the tumor, double or triple cryotherapy is administered to the underside of the conjunctiva (adjacent to the

resection) and the scleral bed [17]. Cryotherapy as primary therapy can also be performed with newly designed cryoprobes [23].

Fig. 8.1 A retinal cryoprobe. Note the ice ball on the tip of the probe

8.5.3 Intraocular Tumors

Intraocular lesions (such as retinoblastoma and retinal capillary hemangioma) are generally treated using a nitrous oxide retinal cryoprobe (Fig. 8.1). Local (retrobulbar) or general anesthesia (for children) is indicated. Using indirect ophthalmoscopy and scleral indentation, the lesion is isolated (Fig. 8.2). It is frozen under direct visualization such that the resulting ice ball completely encompasses the entire tumor (usually to a temperature of −70 °C). The lesion is allowed to slowly thaw, and the freeze-thaw cycle is repeated twice [20]. The tumor is reexamined in 3–4 weeks and may require additional therapy (Fig. 8.3). Most lesions can be treated transconjunctivally; however, those significantly posterior to the equator may require a conjunctival incision [20].

8.6 Complications

While cryotherapy is generally safe and effective, there are numerous complications that must be considered [24]. In most instances, transient edema and injection occur at the site of treatment. Lesions on the eyelid and close to the lash margin can develop ptosis, trichiasis, and ectropion.

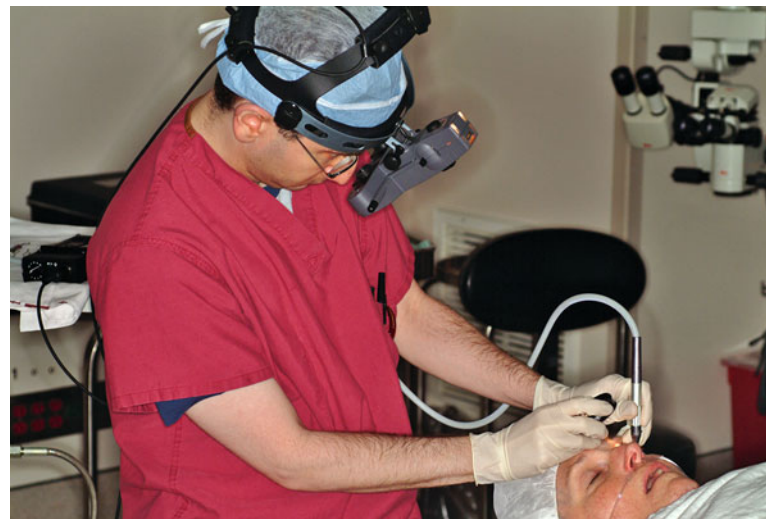

Fig. 8.2 Technique for transcleral cryotherapy of an intraocular tumor under indirect ophthalmoscopic visualization

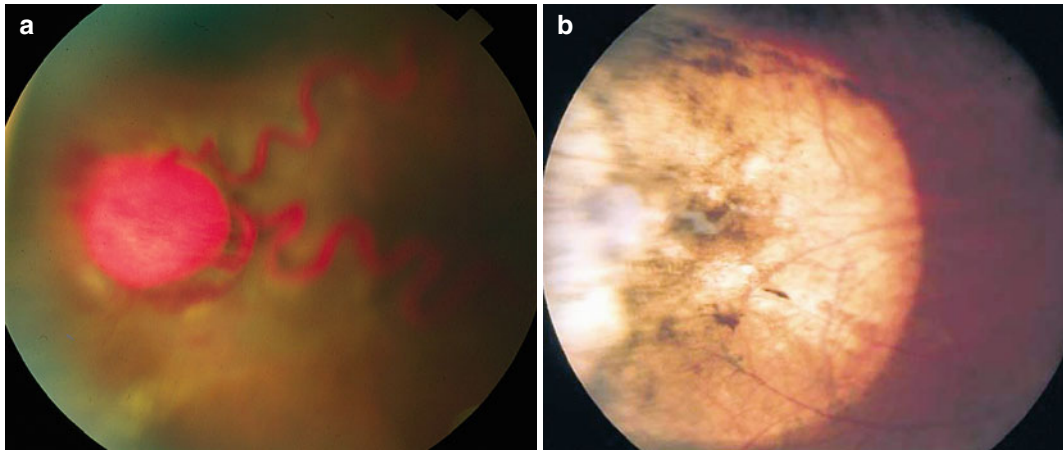

Fig. 8.3 (**a**) Retinal capillary hemangioma treated with cryotherapy. (**b**) Ten months later, the hemangioma appears as a gliotic nodule in an area of chorioretinal atrophy (Reproduced with permission from Singh et al. [25])

Hypertrophic scarring can occur as can skin depigmentation in darker patients.

The conjunctiva generally tolerates freezing well. However, repeated application can lead to limbal stem cell failure, dry eye, and symblepharon formation. Periocular edema and pain are not uncommon following cryotherapy of intraocular lesions. Uveitis may develop requiring the use of topical steroids. Cryotherapy can increase the risk of exudative and rhegmatogenous retinal detachments as well as vitreous hemorrhage. Muscle paresis and changes in pupillary response have also been described.

Conclusions

Cryotherapy is an excellent means of treating certain intra- and periocular tumors. In ophthalmic oncology, this generally translates to high cure rates and minimal ocular morbidity. Cryotherapy is effective in treating small and well-defined tumors. Good technique is critical, with a rapid freeze and slow thawing being most effective in causing the cell death. Multiple freeze-thaw cycles further increase treatment effectiveness. When indicated, cryotherapy can serve as an alternative to more destructive treatment modalities such as surgical excision, chemotherapy, and radiation therapy.

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