

Cryotherapy for Equine Skin Conditions

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Cryotherapy is the controlled use of freezing temperatures to destroy undesirable tissue while doing minimal damage to surrounding healthy tissue. Conditions in which cryotherapy may be indicated include certain skin lesions; ophthalmic, orthopedic, and respiratory tract disorders; and cryoneurectomy. This chapter focuses on the use of cryotherapy for specific skin conditions. One should have a thorough knowledge of the basic principles, freezing agents, cryosurgical units, techniques, and clinical applications before using cryotherapy. Cryotherapy is most useful for small localized skin lesions treated on an outpatient basis.

PRINCIPLES OF CELL DESTRUCTION

Understanding the basic principles of cryotherapy is fundamental to a successful outcome. Cell destruction is best accomplished with rapid freezing, slow thawing, and three freeze-thaw cycles. Cell death is a direct result of ice crystal formation, intracellular fluid and electrolyte disturbances, denaturing of cell membranes, and thermal shock. These factors act dynamically to cause overwhelming cellular pathology. Three major categories of events—immediate, delayed, and late—occur at the cellular level after the application of low temperatures to tissue. Within the immediate phase, there is the abrupt transformation of the intra- and extracellular fluid into ice crystals, which causes dehydration and toxic concentration of electrolytes. Ice crystal formation harms the cell membranes and organelles, causing disruption of their normal function. Freezing denatures proteins and lipoprotein complexes in the cell membranes, leading to cellular swelling and bursting. Other biochemical functions are destroyed by the thermal shock. Cell death is associated with the rate at which tissue is frozen and allowed to thaw. Rapid freezing causes more severe intracellular dehydration but smaller ice crystal formation than with slow freezing. These crystals are physically less disruptive than large ice crystals. The small crystals convert into large crystals if the tissue is allowed to thaw slowly. Therefore, in clinical use, the most effective approach for maximal cellular destruction is to freeze the tissue as rapidly as possible and allow it to thaw slowly, at room temperature, to 0°C.

The delayed phase occurs during the hours following the freeze-thaw cycle. Additional cell death occurs as a result of vascular stasis and endothelial damage. Thrombosis and ischemia produce cell death beyond direct cryogenic damage. In the late phase of cryonecrosis, there is evidence to support an enhanced immune response against tumors from the formation of antibodies and through cell-mediated

responses as a result of cryotherapy. Regression of distant lesions following cryotherapy of isolated equine sarcoids and papillomas has been reported.

FREEZING AGENTS

Liquid nitrogen is the most popular freezing agent for cryotherapy. It is a clear, colorless, odorless, nonflammable liquid that produces a temperature of -195.8°C (-320.5°F). Liquid nitrogen can usually be obtained from medical supply companies that sell oxygen. It is easily poured from the vacuum-insulated flask into the cryosurgical unit. Liquid nitrogen can be kept active for a limited time, usually a maximum of 2 to 4 weeks, if the original container is opened only a few times.

Nitrous oxide is the second most popular freezing agent and is most effective for removing tumors less than 3 cm in diameter or for treating superficial skin lesions. Nitrous oxide does, however, require cryosurgical units specifically designed for its use. Applied with probes, it produces a temperature of -89°C (-138°F). Although more expensive on a unit basis than liquid nitrogen, there is minimal waste with nitrous oxide, and therefore greater efficiency. Nitrous oxide is readily available in veterinary hospitals that use gas anesthesia. One large tank can be used for many months because it usually connects directly to the unit rather than being poured, as with liquid nitrogen.

CRYOSURGICAL UNITS

Cryosurgical units deliver their freezing action by spray or probe. Cryoprobes use the Joule-Thompson effect: rapid expansion of gas under pressure provides low temperatures. The probe is held against the tissue to be destroyed. A phase-changing probe is the method used with nitrous oxide. Liquid nitrogen can be applied with a solid contact probe. A great variety of probes is available, each for a different purpose.

Currently, there is a trend toward the use of spray units. Some units look like modified insulated ("thermos") bottles with a spraying tip at the top.° A mixture of liquid and vaporized liquid nitrogen is sprayed directly onto the area to be treated. Different spray devices deliver different mixtures of vapor and liquid. This can vary from 15% vapor and 85% liquid to 55% vapor and 45% liquid. The higher the percentage of liquid in the spray, the lower the temperature and the more potent the freeze. The amount of

[°]The Cryogun, Arista Surgical Supply Co. Inc., New York, NY

cryogen applied is controlled by valves and/or aperture sizes on the spray tips. This technique allows larger and deeper areas to be frozen at a faster rate. Care must be taken to avoid adjacent tissue damage. Freezing too rapidly or too extensively can lead to cryogen runoff, freezing too deeply, or increased lateral spread of freezing before adequate tissue depth is achieved. Protection of healthy tissue is possible through the use of air foam cups with a hole cut in the bottom to fit the lesion's shape, metal or plastic spray cones, and petroleum jelly applied to normal tissue around the periphery of the lesion. Rapid freezing rate may cause poor visibility because of the production of liquid nitrogen vapor. Application precision can be improved by debulking the lesion prior to cryotherapy and by recording the temperature at the margins and base of the lesion by the use of cryosensors or thermocouple needles.

CRYOTHERAPY TECHNIQUES

Patients receiving cryotherapy should have received recent tetanus vaccination. The procedure can usually be performed in the standing horse sedated with xylazine and butorphanol with or without local infiltration of anesthetic. In some cases, the procedure may require general anesthesia. The site requiring treatment should be cleaned and the hair clipped. Core or segment biopsies of the lesion should be taken the day before cryotherapy, if possible. The biopsy site provides a hole for insertion of the cryoprobes. Surgical debulking of skin lesions, where applicable, improves the efficiency of spray freezing by flattening the irregular surface of the lesion. After biopsy or debulking, hemostasis must be achieved by use of a tourniquet, ligature, direct pressure, or packing the wound.

Most tissues are adequately destroyed by two well applied freeze-thaw cycles. However, increased vascularization, cellular density, and large areas of tissue dilute and impede penetration of the freezing agent and the lesions require more freeze-thaw cycles. The area of cryonecrosis that results is in direct relation to the duration of the freeze. Damage to vital structures such as nerves, blood vessels, and tendons underlying the cryolesion can be minimized by sound anatomic and surgical knowledge and cryotherapy experience. The need for cryosensors depends on the size, shape, and location of the lesion, and the experience level of the operator. It is desirable to freeze a margin of 5 to 10 mm of normal tissue around most malignancies.

Postoperatively, there is considerable local edema and swelling, although bandages and antibiotics are rarely necessary. Swelling resolves in a few days but can be accompanied by a serosanguineous discharge caused by transient vasodilation, especially if the area was previously ulcerated. Hemostasis is excellent postoperatively except where larger vessels have been cut preoperatively through debulking or biopsy. The previously frozen tissues begin to separate from healthy tissues at 4 to 7 days and are occasionally associated with discharge. Use of a fly repellent may be indicated. Usually a dry, hard scab forms, which should be allowed to remain as temporary protection for as long as possible. At approximately 4 weeks after cryotherapy, the scab separates, exposing the granulation bed. The exposed granulation bed heals by secondary intention. The time for

complete healing depends on the size and depth of the cryolesion but is usually 14 to 21 days after the scab disappears. Scarring is minimal but some depigmentation may occur.

CLINICAL APPLICATION

Cryotherapy has advantages over surgical excision in many situations. Cryotherapy is often superior for removal of large lesions such as sarcoids on the lower portion of the leg where poor skin mobility prevents closure with sutures. Conventional surgical excision often produces excessive blood loss, whereas cryotherapy usually results in minimal hemorrhage. This is particularly effective in old or debilitated patients. After cryotherapy, scarring usually is slight, and the cosmetic effect is good. Selective destruction of diseased or neoplastic skin is possible with little damage to normal tissue. Chances of tumor cells spreading from premalignant lesions are reduced. The delayed phase of cryotherapy may provide an immunotherapeutic effect on malignant neoplasms.

Disadvantages of cryotherapy are also recognized. The surgeon performing cryotherapy needs to be experienced in its use. The necrosis and sloughing of frozen tissue may be visually unpleasant and malodorous for 2 to 3 weeks following treatment. Regrowth of white hair near the cryotherapy site sometimes leaves a cosmetic blemish. If the application is too aggressive, vital structures surrounding the frozen lesion may be damaged. This applies especially to blood vessels, nerves, tendons, ligaments, and joint capsules. Large blood vessels frozen during cryotherapy for tumor destruction may start bleeding 30 to 60 minutes later when postoperative attention has been relaxed, or several hours later when a veterinarian is not present.

Skin conditions amenable to cryotherapy include cutaneous neoplasms, usually sarcoids, squamous cell carcinomas, papillomas, and melanomas; exuberant granulation tissue; habronemiasis; and pythiosis. Sarcoids and squamous cell carcinomas are the two conditions in horses most commonly treated with cryotherapy.

The equine sarcoid, the most common tumor of the horse, is a locally invasive, nonmalignant, fibroblastic tumor of the skin. Young horses have a higher incidence of sarcoids with about one third of these having multiple lesions. No predilection for gender or breed exists, and the most common sites are the lower limbs, axilla, ventral abdominal wall, prepuce, groin, ears, periocular region, and commissure of the mouth. Sarcoids are notoriously difficult to treat and rarely undergo spontaneous regression. Regression of distant lesions has been reported following cryosurgical removal of only a few sarcoids. Unless directly adjacent to vital structures, cryotherapy is the treatment of choice for equine sarcoids. Cryotherapy is one of the most effective treatments to prevent recurrence of sarcoid tumors, with 80 to 90% reported cure rates at 12 months later. Conventional surgical excision with or without electrocautery can be followed by local recurrence in up to 60% of the cases.

Success of sarcoid removal was found to be higher after three, rather than two, freeze-thaw cycles. It may be necessary to repeat cryotherapy to attain a higher rate of success. Large lesions should be surgically debulked before freez-

ing. Debulking the sarcoid followed by pressure bandaging can be done the day before cryosurgery if hemorrhage is anticipated. When treating lesions on the lower limb, freezing of the underlying periosteum and bone should be avoided. Because sarcoids are skin lesions, retention of subcutaneous mobility is a good indication that the deeper tissues are being spared. Around the eye region, care should be taken to avoid excessive freezing and complications of eyelid scarring. Other forms of therapy such as intralésional cisplatin (see below) should be considered for sarcoids in this location. Sarcoids that recur following cryotherapy may be refrozen or frozen in conjunction with other types of therapy.

Cryotherapy is a common form of treatment for tumors of the eye, orbit, nictitating membrane, and conjunctiva. In horses, this form of treatment has been used successfully for early ocular squamous cell carcinoma. Squamous cell carcinoma is a malignant tumor arising from the squamous layer of the epithelium. It is the most common ocular neoplasm in the horse. The healing time can be slow but the cosmetic appearance is usually good. In cattle, cryotherapy reportedly has a 70 to 90% success rate for early stages of ocular squamous cell carcinoma. Radical surgical excision and radiation therapy may be preferred for more extensive lesions.

Squamous cell carcinoma in horses also has a predilection for mucocutaneous junctions, such as the eyelids, lip, nose, vulva, prepuce, and penis. Cryotherapy is a successful form of treatment at these sites, as long as the condition is diagnosed and treated early. Cryotherapy has several advantages over conventional surgical excision or amputa-

tion in treating squamous cell carcinoma of the penis. With cryotherapy, the procedure is relatively simple and quick, there is minimal hemorrhage or infection, and there is a lower recurrence rate. It may also allow the continued use of the stallion. Regardless of the site, squamous cell carcinomas are frequently ulcerated, bleed easily, infiltrate extensively at their base, and slowly metastasize. The prognosis for complete resolution is diminished with locally invasive tumors or in the presence of metastasis to regional lymph nodes.

Although a clinically important form of therapy for specific uses, cryotherapy is not a total replacement for conventional surgery. The appeal of cryotherapy is convenience and cost effectiveness. As improved units are manufactured, with some that are designed especially for veterinary application, the practitioner will find it easier to select the proper cryosurgical apparatus and use it effectively.

Supplemental Readings

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Cisplatin Treatment for Cutaneous Tumors

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The use of systemic chemotherapy in equine oncology is limited because of substantial toxicity and cost. Intratumoral chemotherapy consists of injecting anticancer drugs directly into the tumor and adjacent tumor bed. The intratumoral route of administration results in very high drug concentrations in the tumor and tumor bed, and very low concentrations in surrounding normal tissue and plasma. The high tumor-to-plasma drug concentration ratio achieved results in enhanced antitumor activity with no systemic toxicity. Direct administration of the drug into the gross tumor allows optimal local distribution of drug. By comparison, systemic chemotherapy relies on the blood supply to transport and distribute the drug in the tumor. Intratumoral chemotherapy allows the safe use of high-potency anticancer drugs at a reasonable cost in horses because small amounts of drug are used.

The choice of cisplatin for intratumoral chemotherapy

in the treatment of equine cutaneous tumors is based on its wide spectrum of activity against solid tumors including all cutaneous carcinomas, sarcomas, melanomas and lymphomas; long response duration observed after treatment; and its relatively low cost. Cisplatin or *cis*-diamminedichloroplatinum is a heavy metal compound that inhibits deoxyribonucleic acid (DNA) synthesis by directly binding to DNA, which leads to death of actively dividing cells.

TECHNIQUE OF INTRATUMORAL CHEMOTHERAPY

Drug Formulation

The pharmacokinetic advantage of intratumoral chemotherapy is optimized by increasing the time of drug expo-

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