

## An interesting treatment avenue in dermatology

The use of cold in medicine is more than 2000 years old. Widely used for human dermatology, more so since the beginning of the sixties, cryotherapy has not found its place yet in veterinary medicine because the high cost of available devices makes it less than profitable for that purpose.

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Cryotherapy consists in using extreme cold temperatures to eliminate unwanted tissues. Some of its advantages include but are not limited to the fact that it usually does not lead to bleeding and results with very little damage to neighboring tissues. The effects of cryotherapy are closely related to: the nature of the treated tissues, the in situ applied temperature and the repetition of the applications. Cryotherapy (T at least  $-20^{\circ}\text{C}$ ) applies to external tissues and it is therefore not practical for the treatment of lesions that are too large in size unless the possibility to implant a probe within that lesion is established. Therefore, in case of topical use, cryotherapy is useful only for lesions no larger than 1 cm across and no deeper than 5 mm.

To ensure optimal efficacy on tissue removal, treatment must follow a 3 step procedure: an initial step for which the refrigerant gas is applied that leads to "whitening" (burning) of the exposed area; followed by a Thawing phase (usually longer) to allow for optimum effectiveness of the freezing process; and lastly a second application of the freezing treatment. For larger lesions, it might be useful to add another thawing -freezing cycle.

A number of refrigerant gases are available. Liquid nitrogen (which allows for extreme cold temperature to be reached,  $-189^{\circ}\text{C}$ : probe exit temperature) might appear ideal but the equipment involved in its use can be cumbersome and especially costly to maintain. It is therefore favored only by dermatologists and surgeons accustomed to it and with a large enough volume of patients.

Gases such as NO, N<sub>2</sub>O and CO<sub>2</sub> are also available for the same purpose. Although they can only reach temperatures as low as  $-89^{\circ}\text{C}$ ,

one of the advantages is that they are available in a number of convenient formats and at lower cost and therefore more accessible for veterinary use. Also, despite their weaker freezing potential (as compared to liquid N<sub>2</sub>), they can be useful in case of superficial -small lesions.

### Cryotherapy: mode of action

Its mechanism of action can be divided in 3 major phases.

The first phase, instantaneous, occurs at the time of the first refrigerant gas application. It allows for a sudden freezing of the exposed tissues followed by its rapid thawing. The action of cold causes the extra-cellular water to crystallize, leading to localized hyper-osmolality and leakage of intra-cellular water with rise in toxic electrolytes and cellular damage. Thawing of the crystals leads to further cellular damage. Finally, this phase is accentuated by the protein denaturation and the thermal shock that ensues.

The second delayed phase takes place few hours post-refrigerant as application. It is characterized by vascular stasis leading to thrombosis, localized ischemia, modification in pH and eventually cellular death.

The last phase starts several days after treatment. It consists mostly of an immunological response with a localized increase in immune response.

### Cryotherapy: indications

There are multiple human uses: lentigo, keloids, psoriasis, seborrheic keratosis, warts, condylomata acuminata, etc.. It is mostly recommended for common wart removal, external genital warts, lentigo and basal cell carcinomas.

For companion animals, a number of publications outline the usefulness of cryotherapy for the treatment of certain cutaneous tumors, epidermal naevi, peri-anal fistulas, lick dermatitis, etc.

Peer reviewed publication confirmed the effectiveness of cryotherapy. Podkonjal et al. treated melanoma, skin carcinoma, papilloma, "basaliomas", "hemangiomas", "hystiocyomas" and "trichoepitheliomas" with 86% success rate after one treatment and up to 93% after two treatments. They also suggested the use of cryotherapy for the treatment of follicular cysts, granulation tissues, proliferative ear infections, hyperplasia of supracaudal gland, perianal fistula and analom circum. In a recent study, De Queiroz and al. treated 47 cases of cutaneous neoplasm in dogs (20 cases) and cats (10 cases). Tumors were submitted to 2 or 3 freezing / thawing cycles per treatment cycle. Remission was obtained in 98% of cases up to one year post-treatment. Adverse events reported included edema, erythema and post-treatment pain.

The proven targeted action of cryotherapy for the destruction of epithelial cells allows to consider its use for the practical size reduction of certain cutaneous growths. Cryotherapy can also be envisioned as a companion therapy for some "erosive or fistula-linked cutaneous diseases" to stop or reduce dermatitis.

Devices available that deliver a -89°C temperature should only be used for small and shallow (thin) lesions (< 1 cm). For more extensive lesions, liquid N2 should be used instead.



Sebaseous adenoma (dog: crossbreed)



Papilloma (dog: dog de Bordeaux)



Sebaseous adenoma (cat)

Feline and canine cryotherapy application examples:  
(see photos 1 - 3)

- Warts
- Benign neoplasms\*
- After surgical removal of cutaneous neoplasm: removal of additional peripheral tissues
- Kéloïds
- Granulomas
- Lick dermatitis (skin irritation-wound resulting from excessive self-licking)
- Lentigines
- Actinic keratoses
- Peri-anal fistulas

*\*Examples: papillomas, sebaseous adenomas, perianal gland tumours, ceruminous gland tumours, hemangiomas*

The practitioner shall be aware of the contra-indications. They are linked to the action mechanism (selective destruction of tissues) but also to the type of treated indications (malignant tumors has to undergo a surgical resection).

Contra-indications:

- Malignant skin tumours
- Cutaneous necrosis
- Sensitive fingers / paws' extremities\*

*\*risk of trauma to the peripheral arteries and distal necrosis*

## Cryotherapy: practical use - implementation

Before initiating treatment, it is important to remember that cryotherapy is only effective if one strictly follows a specific treatment cycle: in general 2 treatments iterations are necessary to yield optimal results. In some cases, a third treatment might be applied (the treatment frequency must be adapted in relation to the evolution of the treated lesion after the first treatment). With every cycle, it is necessary to at least successively apply the cryogenic gas twice; giving a few seconds delay between each application (this sequence of freezing/thawing/second freezing is crucial to maximize therapy effectiveness).

The depth of the freezing event and therefore the efficacy of cryotherapy depends on the application time and the distance at which the spray is held from the treated area. In general, cryotherapy is more efficacious on thin lesions: it is therefore important to rapidly treat such lesions that might otherwise become too large and as a result require surgical removal instead.

Table 1 displays suggested application times for the device CryOmega® as an example. Total application time should never exceed 30 seconds, allowing for the presentation of «collagenic tissues» which leads to optimal scarring (wound healing).

Size (depth) of the lesion	Suggested time for the 1 <sup>st</sup> application (1 <sup>st</sup> freezing)	Pause time (thawing)	Suggested time for the 2 <sup>nd</sup> application (2 <sup>nd</sup> freezing)
1 mm	5	10	3
2 mm	5	10	3
3 mm	7	12	5
4 mm	8	12	5
5 mm	9	15	6
6 mm	10	15	6

*(These time lengths are given as a guideline: they depend on the type of lesion and therefore must be adapted by the practitioner)*

Shaving of the treated area might be required to allow for easy access by the treating physician prior to the application of the cryogenic gas. The skin must be cleaned by gentle rubbing with a pad soaked with distilled water or physiological fluid and then drying. The cryogenic device must be held vertically just above the lesion (photo 4)

Freezing begins instantly after application and can be immediately seen as a whitening of the treated tissues. (photo 5)



Positioning and upright application of refrigerant gas.



After application, a «whitening» of the treated area is observed.

The «perilesional area» must be treated on a 1-2 mm wide area at the base of the lesion. The device is then gently moved over the entire area to be treated by brush like concentric moves. Per cycle, at least 2 applications are necessary.

To evaluate the clinical response, a control visit must be scheduled 15 to 20 days after the first treatment session. If no evolution of the lesion is noted, it means that it was not responsive to cold, too thick or that the procedure was not optimally followed. It is then probably preferable to follow another therapeutic approach. If the lesion size was reduced but not sufficiently, another therapy session must be executed followed by another control 2 to 3 weeks later. If the lesion is completely gone, or its size reduction judged sufficient by the physician and the pet owner, the treatment is stopped. What is important is the repetition of cycles and applications - that is the total number of applications - more so than the interval between applications (photos 6 -8).



6

Sebaceous adenoma before treatment (dog: carlin)



7

Same lesion as Photo 6 but immediately after treatment



8

Same lesion as Photo 6, 3 weeks later: nodule is now gone and a scab is present (normal healing process).

### Cryotherapy: side effects

What the pet owner should be warned about (potential adverse events):

- Localized swelling with erythema is possible,
- Localized pain
- «vesiculation» with scab formation

These side effects disappear within 72 hours but might sometime require localized treatment. An appropriate anti-inflammation ointment can be used to alleviate some of those symptoms.

Complication	Comments
<b>COMMON</b>	
• pain	• usually during application course
• «vesiculation» (probably blistering)	• few hours post application
• edema and swelling	• few hours post application
• hypopigmentation	• usually on dark areas
• lack of hair regrowth	• rare if application is < 30 sec.
<b>RARE</b>	
• hemorrhaging	• if freezing is too intense
• infection	• improper cleaning of treated area
• necrosis	• if freezing is too intense
• hypertrophic scarring	• if freezing is too intense

### Conclusion

Cryotherapy is a useful tool for both human and veterinarian dermatology but one has to clearly identify proper indications, uses and be in full control of its implementation. It cannot replace conventional surgery and must be considered as a complementary tool in treating cutaneous lesions. Its effectiveness is greatly increased when applied to an early stage lesion of small size. Pet owners are often enthusiastic about this therapeutic approach because it is perceived as being non-invasive, almost «pain free» and does not require anaesthesia. It is however important for the physician to clearly identify its advantages and disadvantages.

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