

Review Article

Intralesional Cryosurgery for Keloids, Hidradenitis Suppurativa, Basal Cell Carcinomas, and Cutaneous Metastases: A Review

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Abstract

Recently, the uses of intralesional cryosurgery (ILC) have been rapidly expanding in the field of dermatology and oncology. Thus far, ILC has been effectively used to treat keloids, hidradenitis suppurativa (HS), basal cell carcinomas (BCCs), and cutaneous metastases. These conditions can be difficult to treat so it is significant to have an alternative, effective treatment option available. ILC has several advantages over other treatment options for these conditions such as the method's simplicity, cost-effectiveness, and lack of side effects, pain, and complications. This manuscript reviews data concerning the use of ILC in the treatment of keloids, HS, BCCs, and cutaneous metastases.

ABBREVIATIONS

ILC: Intralesional cryosurgery; **HS:** Hidradenitis suppurativa; **BCCs:** Basal cell carcinomas; **cm:** Centimeters; **mm:** Millimeters

INTRODUCTION

Spray cryotherapy has been used in dermatology for many years, most commonly treating benign and precancerous lesions with a few examples being verruca vulgaris, molluscum contagiosum, irritated seborrheic keratoses, and actinic keratoses. Intralesional cryosurgery (ILC) was first introduced in 1993 and has recently gained popularity in dermatology and oncology [1]. A few of the main disadvantages to surface cryotherapy (spray and contact varieties) are edema and hemorrhagic bullae at the treatment site, which can take up to two months to heal [2]. Another considerable disadvantage with surface cryotherapy is the inability to freeze beyond 2 centimeters (cm) in depth with the contact technique and 1 cm in depth with the spray technique [3].

ILC was developed to overcome these disadvantages. Edema and hemorrhagic bullae are seen with ILC as well, however, they are less severe and heal quicker because the freezing is mostly concentrated below the epidermis rather than occurring through the epidermis. The cosmetic outcomes of ILC are superior to traditional cryotherapy as well; hypopigmentation is very commonly seen with traditional cryotherapy but not with ILC. This is important when using cryotherapy to treat lesions with cosmetic implications, such as keloids and for treating malignant lesions in cosmetically sensitive areas, such as BCCs on the face.

In the last few years, ILC has been used in dermatology to treat keloids [4], hidradenitis suppurativa (HS), and basal cell carcinomas (BCCs) [5,6]. ILC has also been used to treat numerous types of cancers and metastases, including cutaneous metastases from primary breast cancer [7]. The uses for ILC are rapidly expanding.

METHODS

PubMed electronic searches were performed using combinations of the following terms: "cryo", "cryosurgery", "cryotherapy", "intralesional", "cryoinsufflation", "keloid", "hidradenitis suppurativa", "treatment", "basal cell carcinoma", "metastatic cancer", and "cutaneous metastases". The resulting works were systematically reviewed as well as relevant articles cited in their references section, considering only literature written in English.

HOW IT WORKS

ILC destroys lesions through tissue anoxia [4] Extracellular ice crystals are formed which pulls water out of the cells and leads to intracellular ice formation, which causes cell death and clotting in the blood vessels [8]. Cryotherapy also has additional antitumor effects. When cryosurgery was used to treat primary prostate tumors, the authors found that the metastatic lesions also resolved but with no treatment [9]. It has since been found that cryotherapy causes a release of tumor antigens and inflammatory markers. A T-lymphocyte response is triggered and the activity of natural killer cells is increased, which ultimately has an antineoplastic effect [9,10].

ILC METHODS

ILC has been performed using a few different techniques. Lumbar puncture needles and curved needles have been used to treat keloids [11]. Recently a needle probe specifically for ILC has been developed. The probe is a long, uninsulated, double-lumen needle with a sharp distal tip, cryogen vent, and adapter so it can be connected to a cryogen source [12]. ILC is performed under universal sterile precautions, which is different from traditional cryotherapy. The lesion is first anesthetized using local anesthetic and then the probe is inserted. For keloids and BCCs, the probe is inserted completely from one end of the lesion until it exits at the other end [4,6]. Liquid nitrogen is then passed through the probe until the lesion appears visually frozen for keloids, or until a visually frozen halo appears beyond the clinical borders of the lesion for BCCs. The halo is typically 2 to 5 millimeters (mm). The freezing process can take from ten to sixty minutes [4,6]. One or two freeze-thaw cycles have both been used successfully for BCCs, while one cycle is currently used for keloids [4,6,13].

Cryoinsufflation is an extremely similar procedure in which liquid nitrogen is injected intralesionally, but in this procedure, through a regular needle. An adapter is necessary to mount the needle onto the cryosurgery unit. This method has been used for HS. In this procedure, a 21-gauge needle is partially inserted into the abscesses and sinus tracts causing the liquid nitrogen to disperse and fill all the connecting tracts. The pulsing technique, rather than constant flow, is used here so that the pressure does not build up too much and cause significant pain to the patient. A pulse of five seconds with a one second pause repeated three times is the method that has been described [5].

For breast cancer metastases, a cryoprobe (3 or 5 mm in diameter) was inserted into the center of the tumor mass using ultrasound or computerized tomography guidance and frozen using an argon gas-based cryosurgical unit. Two freeze-thaw cycles were completed, each reaching a temperature of -180 degrees Celsius at the tip of the probe, with ice ball formation that extended 1 cm past the tumor determining the length of freezing. Fibrin glue was inserted into the tract after probe removal to ensure adequate hemostasis [7]. For this method and aforementioned methods, multiple probes were used for larger tumors/lesions, in the center and periphery of the lesions, to ensure complete freezing took place.

ILC TREATMENT OF KELOIDS

Keloids are a common complaint of dermatology patients and are met with many difficulties during treatment. Intralesional corticosteroids are typically first line but are not always effective, with many lesions recurring after treatment. Contact cryotherapy has been used as well but often requires a significant number of treatment sessions [14]. ILC has been found to be a very effective therapy for keloids. One of the benefits from ILC compared to contact cryotherapy is that hypopigmentation is rare with ILC while it is the most common side effect seen with contact cryotherapy. ILC has been shown to be superior to contact cryotherapy with better results, shorter healing time [4], and decreased pain for the patient [15]. Additionally, a pain control protocol has been developed which can aid in further

reducing pain during cutaneous cryosurgery [15]. ILC has also been found to transform the architecture of the scar to resemble a more normal dermis when analyzed histologically [16].

There have not been any trials comparing intralesional corticosteroids to ILC so more information is needed in order to determine if ILC is more effective than intralesional corticosteroids. However, intralesional corticosteroid injections are easier and faster to do so will likely remain first line but ILC is another available, effective option for lesions that are not responding to intralesional corticosteroids.

ILC FOR HIDRADENITIS SUPPURATIVA

HS is a chronic dermatologic condition with deep nodules, cysts, sinus tracts and scarring most commonly in the cutaneous intertriginous areas. Many cases of HS are very difficult to treat and control. Numerous treatments have been used for HS but none have been completely effective and patient's quality of life is often impacted significantly. Antibiotics, biologic agents, and surgeries are just a few examples of treatment options for HS [17]. A recent case report reported the use of cryoinsufflation to successfully treat HS in two patients. One of the reported patients had severe, recalcitrant HS whom was also pregnant. The majority of the available treatment options are contraindicated in pregnancy, which led to very limited treatment options for this patient. Of note, this patient had previously failed more conventional treatments before she became pregnant. Another patient experienced significant adverse events from multiple different antibiotics and early recurrence even after surgical excision and therefore was treated with cryoinsufflation as well [5].

Monthly treatment sessions took place for these patients for 3 months, which allowed focused scarring of the abscesses' and sinus tracts. No recurrence was seen for up to six months. These patients were very satisfied with the results. However, both patients experienced a vagal reaction with nausea, sweating, and weakness during the treatment. These patients also received paracetamol prophylactically for the first 24 hours to help with any delayed discomfort, however, the patients did not complain of pain [5].

Traditional cryotherapy has been used for HS in the past but the results were poor. Patients experienced significant pain during and after the treatment, and the majority of patients treated in this way also developed ulcerations and infections [18]. ILC appears to be very promising for HS. However, more research is necessary to compare ILC to other therapies but thus far it appears to be extremely safe and effective, and is another option to keep in mind for recalcitrant patients.

TREATMENT OF BCCs WITH ILC

Currently, the preferred treatment for BCCs is surgical excision, Mohs micrographic surgery, and electrodesiccation [19]. Traditional cryotherapy has been used and effective for BCC in the past, with cure rates of 95-99% [20]. However, contact or spray cryotherapy is not as effective for BCCs as ILC because the depth of penetration is not deep enough with the traditional methods to be able to eradicate larger lesions in one or two treatments, therefore is most useful for small BCCs [6]. A

recent study was done on ILC for primary, superficial or nodular BCCs on the head and neck that did not exceed a surface area of 5cm². For this technique, Weshahy's cryoneedles were used, which are angled or hook shaped needles. Using this method, 97.8% cure rate after one treatment occurred for small and medium sized BCCs, which they classified as BCCs with surface area less than 5cm². This is similar to the cure rates for other currently acceptable treatment modalities [6]. There has also been a recent reported case of successful removal of two BCCs on the lower leg of an individual using ILC [13]. Surgical excision for BCCs on the face and neck are often complicated. In these areas where surgical excision is difficult, intralesional cryosurgery is a very useful alternative. The complications seen with ILC for BCC were minimal. One patient experienced a wound infection, but other, more serious complications were not reported. ILC is also a relatively cheap option in comparison to the other treatment modalities, especially compared to Mohs micrographic surgery. It is also a relatively simple procedure to perform in comparison to other surgical treatments for BCCs and patients who are poor surgical candidates [6].

ILC FOR CANCER METASTASES

Prostate cancer [19]. Recently, ILC has been used for treating metastases of breast, hepatic, non-small cell lung, and esophageal cancers [7,22-24]. The hepatic, non small cell lung, and esophageal cancer patients did not have cutaneous metastases that were treated, however ILC treatment was superior to the treatment with chemotherapy alone with an even higher success rate in some cases if both treatments were used together [22-24].

ILC has recently been used for metastases of breast cancer after radical surgery failed to cure the patients of cancer. Some of the metastases treated were cutaneous, however the authors did not give results for the cutaneous metastases separately from the other metastases treated with ILC. These patients were followed for ten years and it was found that overall survival was higher in the ILC group as compared to the chemotherapy group. Survival time was longer in patients treated with multiple sessions of ILC as compared to just one session. Survival time was also increased in patients treated with ILC immediately after the detection of metastases as compared to those patients treated with ILC over 3 months after the detection of metastases [7].

Adverse events were reported from ILC of pulmonary, bone, and hepatic metastases however adverse events for cutaneous metastases were not reported. Of note, the adverse events that did occur in other organs resolved with minor or no treatment in 1 to 2 weeks [7]. Overall, patients tolerate the adverse events of ILC much better than the typical adverse events associated with chemotherapy which include nausea, vomiting, diarrhea, hair loss, fatigue, fever along with many others.

CONCLUSIONS

ILC is emerging as a very promising treatment modality for dermatology and oncology. ILC has been effective for difficult to treat dermatologic lesions such as keloids and HS, where no treatment modalities is solely effective. For these conditions, it is helpful to have another option to use when patients are not responding to more traditional treatments, and with more research ILC may even become one of the standard treatments

for these conditions.

ILC has shown promising results for many primary tumors and both systemic and cutaneous metastases. Elderly patients, with increased comorbidities, are often at risk of increased complications with surgical procedures. ILC has thus far been free of significant complications. ILC will likely eventually play an important role in treating cutaneous malignancies, especially with respect to the elderly population and even in the palliative care setting.

The cosmetic outcomes when using ILC are superior to that seen with traditional cryotherapy, however more research is needed to compare the cosmetic outcomes to other standard treatment modalities. ILC is very easy to perform and a relatively cheap and quick procedure. More research is necessary in order to ensure the safety and efficacy but from the literature so far, it appears that it is worthy of more dedicated research into its efficacy and also into additional uses for ILC.

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