Nat. Volatiles & Essent. Oils, 2021; 8(5): 13346-13351

NVEO
Natural Volatiles & Essential Oils

General Overview Of Intralesional Cryotherapy In Managing Keloids

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Abstract

Background: Keloid is a dermal fibro-proliferative disorder that occurs due to abnormal wound healing and excessive deposition of collagen. It presents as a raised scar which is sometimes confused with a more common type of scars called hypertrophic scars. The incidence of keloids is highest among darker-pigmented persons of African, Asian and Hispanic descent with an age range from 10-30 years old. Keloids are slightly more common in females, likely due to more cosmetic procedures like ear piercing. Intralesional cryotherapy is a relatively new technique in the treatment of skin lesions which freezes the lesion from the centre outwards. It has been proved to be a safe and effective modality, with few adverse effects.

Keywords: Intralesional Cryotherapy, Keloids

Background

Keloid is a dermal fibro-proliferative disorder that occurs due to abnormal wound healing and excessive deposition of collagen. It presents as a raised scar which is sometimes confused with a more common type of scars called hypertrophic scars **(1).**

Unlike hypertrophic scars, keloids grow into the surrounding normal skin and extend beyond the boundaries of the original wound. keloids are often associated with pain, hyperaesthesia and pruritus that can dramatically affect the patient's quality of life **(2).**

Epidemiology

The incidence of keloids is highest among darker-pigmented persons of African, Asian and Hispanic descent with an age range from 10-30 years old. Keloids are slightly more common in females, likely due to more cosmetic procedures like ear piercing **(3)**.

Risk factors

The mechanism of keloid development and progression is poorly understood. Aberrant wound healing after trauma to the skin e.g. earlobe piercing, surgery, acne, chickenpox, is the primary cause identified for the development of keloids in susceptible individuals. Multiple systemic and local risk factors are thought to promote keloid formation. These factors, together or alone, can induce persistent inflammation in the wound and subsequent scarring. This inflammation leads to chronic fibroblast activity and blocks scar maturation **(4).**

Examples for systemic risk factors include hypertension and pregnancy, which are associated with a higher risk of bulky scar formation. In pregnancy, the vasodilator effect of estrogen may promote the movement of immune factors and cells into the wound, thereby exacerbating local inflammation. In hypertensive patients, it is possible that the strain imposed by hypertension on the existing and newly forming blood vessels in keloids promotes their vasodilation and exacerbates the chronic local inflammation **(2).**

Local risk factors for keloid formation and progression include delayed wound healing, wound depth and mechanical forces such as the skin tension that is induced by stretching**.** This is evidenced by the fact that keloids show a strong predisposition to occur on body areas with strong and/or repetitive stretching of the skin, namely, the anterior chest, shoulder, deltoid, jaw and ear. By contrast, keloids rarely occur in areas where the stretching of the skin is rare, such as the scalp or anterior tibiae. The presence of foreign material, infection and hematoma in the wound can also lead to keloid formation in susceptible individuals **(5).**

Keloid formation and/or progression also is associated with a variety of genetic factors. First, a genetic predisposition was suggested by the fact that keloids are more common in dark skinned individuals and Asians. Moreover, keloid patients often have a family history of these scars **(6) .**

Familial keloid case studies and twin studies support the fact that genetic factors have an influence in keloid etiology. Although no one specific gene has been associated with the development of keloids, a number of genes and gene loci have been identified. Genome-wide association studies have identified single-nucleotide polymorphisms genetically linked to keloid development including the NEDD4 gene, which encodes E3 ubiquitin ligase enzyme, and the myosin genes (MY01E and MYO7A**) (7) .**

Studies have also reported the involvement of human leucocyte antigen (HLA) alleles, p53, BCL-2, and FAS genes. Furthermore, rare genetic disorders have been reported to present with spontaneous keloids including Rubinstein-Taybi syndrome, Noonan syndrome, and Geominne syndrome**.** These lines of evidence suggest that genetic factors play a role on keloid predisposition **(8)**.

Pathophysiology of keloid

Standard wound healing consists of three phases: (1) inflammatory, (2) fibroblastic, and (3) maturation. In keloids, the fibroblastic phase continues, unchecked, resulting in the clinical and histopathological findings. Keloidal fibroblasts have increased proliferative activity, persist for longer period, and have lower rates of apoptosis compared to typical fibroblasts. This results in an overproduction of collagen and cytokines. Collagen synthesis in keloids is 20 times greater than that of healthy skin and three times greater than a hypertrophic scar **(9) .**

Various cytokines, growth factors and proteolytic enzymes have been implicated in the formation of keloids including transforming growth factor-β (TGF-β), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), tumour necrosis factor-α (TNF-α), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-β(FGF-β), interleukin-6(IL-6), interleukin-13(IL13) and matrix metalloproteinases (MMPs) witch are endopeptidases with the primary function of degrading an array of ECM proteins **(10)** .

Along with serine proteinases such as tissue plasminogen activator and urokinase plasminogen activator, MMPs counteract fibroblast production of ECM proteins and provide a balance by preventing excessive matrix synthesis. The degradation of collagen types I, II, and III is mediated by MMP-1 (collagenase 1), MMP-8 (collagenase 2), and MMP-13, respectively. The activity and function of MMPs are also dependent on

several factors that are dysregulated in aberrant scarring pathologies such as hypertrophic scarring and keloids **(11).**

Transforming growth factor- β and PDGF are thought to be the primary drivers of this process. Transforming growth factor- β, an integral part of wound healing, promotes chemotaxis of fibroblasts to the site of inflammation and production of collagen. Dysregulation of this pathway leads to fibrosis and abnormal scar response **(12).**

Intralesional Cryotherapy

Intralesional cryotherapy is a relatively new technique in the treatment of skin lesions which freezes the lesion from the center outwards. It has been proved to be a safe and effective modality, with few adverse effects**.** The technique was initially described by **Weshahy** in **1993** for treatment of skin lesions and by **Zouboulis and Orfanos** in **2000**, for treatment of scars, and was subsequently modified and developed by **Har-Shai et al.,** in **2003 (17)**.

Indications of cryotherapy

Cryotherapy has a number of indications for both malignant and benign lesions .Benign lesions that can be treated with crytherapy include seborrheic keratosis, verruca, skin tags, molluscum contagiosum, solar lentigo and hypertrophic/keloid scars. Most of the entities can be treated with a single round of cryotherapy, but for larger or thicker lesions treatments can be repeated at 3 to 4-week intervals until the lesions have resolved. This is especially true in verruca which typically take anywhere from 2 to 6 treatments to resolve **(14)**.

Pre-malignant and malignant lesions that can be treated with cryotherapy include actinic keratosis, basal cell carcinoma, and non invasive squamous cell carcinoma. Cryotherapy has been used to treat lentigo maligna melanoma with variable efficacy and recurrence rates. However, the treatment of malignant lesions with cryotherapy is not a first-line therapy and is typically reserved for patients who are not good candidates for excision **(15)**.

Intralesional cryotherapy in keloids

Cryotherapy has major advantage of a low relapse rate . However, frequent treatment sessions are required to achieve good results, especially in large keloids, using the contact cryotherapy method **(Butler et al., 2008)**.

The use of external cryotherapy in the treatment of keloids has also been associated with several side effects including hypopigmentation, blistering, pain, delayed healing and infection. Thus, the need for new, more potent, and quickly effective cryotherapy methods and instruments has been recognized. To minimize side effects, intralesional cryotherapy was introduced. This modality was associated with success rates in the range of 32%–74% **(15).**

This technique exhibits an increased efficacy in the treatment of hypertrophic scars and keloids, due to the enhanced freezing area of deeply located scar tissue. In addition, fewer cryotherapy sessions are required and less hypopigmentation is evident following the application of intralesional cryothearpy. It works by destroying the core of the keloid, sparing the surface epithelial cells including melanocytes. As a result, it enhances volume decrease while minimizing the risk of hypopigmentation and other surface reactions **(16).**

Har-Shai et al ., (17) have demonstrated that the intralesional cryoprobe showed a slower cooling rate (20 °C/min), compared to the contact cryotherapy method, with an end temperature of −30 °C. However, the thawing rate was faster (35 °C/min). The hold time, i.e., the time in which the freezing process retained its

lowest temperature, was found to be significantly long (minutes to hours). In addition, the skin did not exhibit marked hypopigmentation. It has been assumed that the end temperature during intralesional cryotherapy and the moderate cooling and thawing rates, are more “friendly” for melanocyte survival.

The histological changes occurring in the scar tissue following intralesional cryotherapy, demonstrated that the architectural pattern of the collagen became more organized, thus, rejuvenation of the scar tissue became evident, which can explain the significantly reduced recurrence rate following intralesional cryotherapy **(18)**.

Intralesional Cryoneedle

Weshahy, (**1993**) was the first to describe a cryoneedle probe which consisted of a curved hypodermal needle with an open tip which was inserted underneath the skin lesion/tumor. **Zouboulis et al.,(2000**). further developed this method by using a long hypodermal needle (20 gauges). Later, **Gupta and Kumar,** (**2001**) have published their experience with intralesional approach by employing simultaneously several hypodermal needles (21 gauges) and/or single-use lumbar puncture (LP) to treat hypertrophic scars and keloids.

The results which have been obtained using these open-ended and thin hypodermal cryoneedles demonstrated suboptimal results which necessitated up to 10 cryosurgical sessions for scar flattening. In**(17), Har-Shai et al.,** have refined the technique by developing a novel intralesional cryoneedle **(**.This probe consists of an elongated double-lumen needle with a safety vent and a sharp-cutting distal tip which enhances the penetration of the often hard keloids. The proximal end of the cryoprobe is connected via an elongation tube to a cryogen source. By forcing liquid nitrogen to circulate through the needle, an ice ball around the cryoneedle developed causing the scar tissue to be completely frozen while the generated gas is dispersed to the atmosphere away from the patient via a safety vent.

Technique of intralesional cryotherapy in keloids

Scar selection

Certain scar types may be preferred, possibly due to better outcomes, or less adverse effects. Keloids with a narrow base may be regarded as ideal scars for this treatment. The narrow base ensures concentration of the cooling effect within the small soft tissue pedicle, thereby maximizing freezing. Broader scars with wider bases, may also be predicted to respond to treatment, but may not display as complete a response as narrow-based, pedunculated keloids **(17)**.

Anaesthesia

The majority of cases may be treated under local anesthesia. Attention to anaesthetic technique in these cases is crucial, as trauma from a hypodermic needle puncture site outside the scar may stimulate formation of more keloid scarring. For this reason, translesional delivery of local anaesthetic is utilized**.** Typically, 0.5% bupivicaine with adrenaline may be used. In very large keloids, a general anaesthetic may be required **(13)** .

Cryoprobe penetration of scar

The skin is prepared with topical antiseptic. The scar itself is grasped between the index and thumb of the other hand, until the sharp tip of the needle penetrates the opposite distal edge of the scar, thus maximizing the volume of scar tissue to be frozen. The cryoprobe is inserted through the middle (core) of the scar, along its long axis. Care should be taken to assure that the vent nostril is positioned away from the patient to

prevent accidental freezing of adjacent skin or tissue. Sterile gauzes are placed between the patient's skin and protruding ends of the cryoprobe, in order to protect these areas from unintended freezing **(13)**.

Freezing process

The cryoprobe is connected to a cryogun containing liquid nitrogen. The cryogun is grasped or placed on a steady surface which is located higher than the scar to facilitate the liquid nitrogen flow with no direct contact with the patient body. By activating the cryogun trigger, the cryogen enters the cryoneedle, thereby freezing the scar. The length of the intralesional cryosurgery process depends upon the scar volume and ranges between 5 min and two and a half hours **(17) .**

Freezing is rapid and may be assessed visually and by palpation. The process continues until the entire scar and a 5–10-mm margin of uninvolved skin are completely frozen. The extent of freezing at the margin is best assessed by palpation of a very distinct, hard, subcutaneous 'shoulder' around the scar base. Therefore, the treatment end-point is determined by physical features rather than a time limit. When this point is reached, nitrogen flow is stopped and the cryoprobe is allowed to thaw before being removed. A sterile non-adherent dressing is applied **(13)** .

Postoperative management

The patients should be instructed to apply an antibiotic ointment until full healing is accomplished. Patients may be given several dressings to apply at home, as it is expected that serous or serosanguinous discharge may be considerable in the week after treatment. After approximately one week, discharge usually ceases and dry necrosis becomes apparent. Shrinkage and desiccation continue for two to eight weeks postoperatively, before separation of overlying eschar, revealing a granulating wound. The wound then heals by re-epithelialization **(13)**.

Adverse effects of intralesional cryotherapy

Pain

Pain has been reported consistently; however, in nearly all cases, this was reported as mild in nature and was easily controlled with short-course oral analgesia. The procedure has been reported as being well-tolerated **(12).**

Prolonged healing

Slow healing times are common with cryotherapy, similar to the effects of frostbite injuries. It would seem that the healing time is of the order of several weeks, but the range is not known **(13)**.

Hypopigmentation

Skin hypo-pigmentation would seem to be an expected adverse outcome in darker skin types treated with cryotherapy**.** It is well-recognized following both spray and contact cryotherapy, however it is significantly less common with intralesional cryotherapy. This is attributed to slower cooling and significantly higher end-point temperatures observed with intralesional cryotherapy than with contact cryotherapy. Post-treatment hypopigmentation is often a temporary phenomenon, with reported recovery of pigmentation in 69–100% of affected individuals **(12).**

Har-Shai et al., **(17)** had examined the cooling characteristics of both intralesional cryotherapy and contact cryotherapy, in relation to subsequent pigmentary changes. In the contact cryotherapy group, 91% of cases

developed significant depigmentation, whereas in the group treated with intralesional cryotherapy, no marked hypo-pigmentation was observed .

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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