The intralesional cryosurgery technique – A new and effective technology for the treatment of hypertrophic scars and keloids

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Introduction

The therapeutic management of hypertrophic scars and keloids (HSK) remains a challenge. In 1982, Shepherd and Dawber were the first to apply cryosurgery as a monotherapy regimen for treating HSK. Although this single cryosurgical session achieved 80% improvement, a high recurrence rate of 33% was observed. Further monotherapy studies were lacking, perhaps indefinitely delayed by the rather disappointing relapse rate, until Mende, Zouboulis and Orfanos and others showed that repeated surface/spray cryosurgical sessions can have a beneficial effect on HSK (between 68% – 81% remission), with almost no (2%) recurrence.

To achieve these results, 1 to 20 treatment sessions using the contact cryosurgery method were required. Thus, the problems associated with commercially available application probes have been documented and the need for improved devices has been recognized. The studies executed and described in this review were designed to assess the clinical safety and efficacy of a new intralesional needle cryoprobe as a monotherapy method in the treatment of HSK.

The intralesional cryoneedle

A novel intralesional cryoprobe (CryoShape™, U.S Patent Number 6,503,246; European Patent Number 1299043, FDA 510(k) Number K060928) was developed [Har-Shai et al (2003); Har-Shai et al (2006); Har-Shai et al (2006)]. This probe
consists of an elongated double-lumen uninsulated needle with a safety vent and a sharp-cutting, sealed, distal tip, which enhances the penetration of the often hard, rubbery, and dense HSK. The proximal end of the cryoprobe was attached to an adaptor, which was connected to a cryogen source. By forcing liquid nitrogen to circulate through the needle an ice ball around the cryoneedle developed causing the abutted HSK tissue to be completely frozen.

**Intralesional cryosurgery method**

With the patient lying in a comfortable supine position, the skin surface of the HSK was cleansed with disinfecting solution and was then draped. The area of penetration into the scar and the underlying subcutaneous tissue was anesthetized locally using an intralesional approach with bupivacaine hydrochloride 0.5% (marcaine). Thereafter, the sterile cryoprobe was forced into the long axis of the scar in a forward awl-like rotary movement parallel to the skin surface. The cryoneedle was inserted at the core of the scar, which was approximately 5–6 mm deep from the skin surface of the HKS.

The scar itself was grasped between the index and thumb of the other hand until the sharp tip of the needle penetrated the opposite distal edge of the scar, thus maximizing the volume of scar tissue to be frozen. Attention was taken to prevent any penetration of the cryoprobe into uninvolved, healthy surrounding skin. Sterile gauzes were placed under the proximal and distal parts of the cryoprobe and care was taken to ensure that the vent nostril was positioned away from the patient to prevent accidental freezing of adjacent skin or tissue.

The proximal part of the probe was connected via a luer lock elongation tube to the cryogun (Brymill Cryogenic Systems, Ellington, Conn), which was filled about 10 to 15 minutes beforehand with liquid nitrogen in order to allow sufficient pressure to build-up inside it (about 0.7 ATM/ 10 psi). The cryogun was placed on a steady surface with no direct contact with the patient’s body. By activating the cryogun trigger, the pressure valve opens and the cryogen enters the cryoneedle, thereby freezing the HKS. A forced stream of liquid nitrogen gas flows out from the vent nostril during the entire freezing process. The strength of the stream flow indicated the efficacy of the freezing procedure. Two ice balls appeared shortly at the two cryoprobe penetration sites and with time they gradually spread towards each other until complete freezing of the scar was achieved clinically.
Following complete freezing of the HKS, regardless of the duration of the cryosurgery process, the cryogun trigger was released to stop the freezing process and the cryoprobe was left to thaw for 1 to 2 minutes and was then withdrawn in a reverse awl-like rotary movement. After complete thawing of the HSK is noticed clinically, slight bleeding from the penetration points of the probe requires the application of a sterile dressing. The patient was then instructed to wash the treated HSK daily and to apply an antibiotic ointment until full recovery of the HKS was accomplished.

Patients and methods
Three different clinical and basic research studies were executed to assess the safety and efficacy of the intralesional cryosurgery technique.

The first study consisted of 95 Caucasian patients (51 females; 44 males), ranging in age from 3 to 67 years, with a total of 112 HSK (chest- 62; auricular and lobular- 26; shoulder- 7; neck- 4; abdomen- 4; breast- 4; nape- 3; arm and forearm- 2) of more than 6 months’ duration and with diverse causes.

The 18-month trial evaluated volume reduction of the HSK following a single session of intralesional cryosurgery. Objective (hardness and color) and subjective parameters (pain/tenderness and itchiness/discomfort) were examined on a scale of 0–3 (with a low score being superior). Pre- and post-treatment biopsies were taken for histo-morphometric studies of the collagen fibers, including spectral Picrosirius red polarization, fractal analysis and Fast Fourier Transform algorithm orientation index. The volume reduction of the scars was evaluated using an Elite H-D Putty Vinyl Polysiloxane high precision (>99.5%) impression material (Zhermack®, Italy) and water displacement method, before and following a single intralesional cryotherapy session. Photographs were taken of all scars. This assessment was done before treatment, 2 weeks, and 1, 2, 3, 6, 12 and 18 months after treatment.

A second study was designed to assess the efficacy and safety of the intralesional cryoprobe in the treatment of difficult recalcitrant auricular keloids and to explore and explain its mechanism of action.

Nine Caucasian patients (7 female and 2 male) aged from 18 to 55 years with a total of 10 auricular keloids (6 months to 6 years old) were included in the study. The
etiology of the lesions was piercing (9/10) and skin laceration (1/10). The location of the keloids was lobular (7/10) and helical (3/10). Previous scar treatment included surgical excisions, laser surgery, surface (contact/spray) cryosurgery, intralesional corticosteroid injections and local application of silicone ointments without improvement.

The 18-month trial evaluated volume reduction of the HSK following a single session of intralesional cryosurgery. Objective (hardness and color) and subjective parameters (pain/tenderness and itchiness/discomfort) were examined on a scale of 0–3 (low score was better). In order to evaluate the possible mechanisms of injury during intralesional cryosurgery, the thermal history of the intralesional cryoprobe was examined at room temperature (isolated) and on a fresh swine muscle model and compared with the contact cryosurgery method.

A third study was designed to compare the thermal history of skin surface temperature during the treatment of keloids using the contact and intralesional techniques and its effect on skin pigmentation. Thirty Caucasian patients with 45 HKS older than 6 months and recalcitrant to at least one other treatment modality were included in this study. Twenty-one HKS were treated by the contact method while the remaining 24 HKS were managed with intralesional cryosurgery. All scars prior to the cryosurgical treatment had no pigmentation changes. Previous scar treatments included surgical excisions, laser surgery, intralesional corticosteroid injections and local application of silicone ointments or sheeting.

Assessment of hypopigmentation was executed 6 months after the treatment by comparing skin pigmentation on the keloid surface with the healthy surrounding skin on a scale from 0 to 2.

The hospital ethics committee approved these studies and an informed consent was obtained from all the patients who participated.

Results
The results of the first study revealed the following:
The time needed to accomplish a complete freezing of the HSK was between 7 to 24 minutes according to the pretreated HSK volume.
A significant reduction in objective parameters (hardness and redness) and alleviation in terms of the subjective complaints of pain/tenderness and itchiness/discomfort were achieved. The average HSK hardness and redness before treatment were 2.8 ± 0.1 and 2.9 ± 0.1 respectively, and at 18 months post treatment, 0.8 ± 0.2, p=0.0022 and 1.4 ± 0.3, respectively; p= 0.011. The average pretreatment pain/tenderness and itchiness/discomfort were 2.3 ± 0.3 and 2.6 ± 0.2, compared with 0.5 ± 0.2, p=0.0051 and 1.0 ± 0.3, p=0.0051, respectively at 18 months post cryosurgery. The average pre-operative HSK volume was 1.82 ± 0.33 (range: 0.3 cc–3.8cc) compared with the average post-treatment volume of 0.95 ± 0.21 following one session of intralesional cryosurgery treatment. The average volume reduction then 51.4 ± 3.2 % (range: 33-67 %; p<0.0022).

The patients complained of very mild pain or discomfort during and after the procedure, which was easily managed. Only mild local edema and epidermolysis/blisters were evident. Neither active bleeding from the penetration points nor infection was documented. No adverse reactions at the cryosurgical site or HSK worsening were noticed during the 18 month follow-up period. Eight of the 112 HSK did not respond to the intralesional cryosurgical treatment.

The ROC analysis revealed that the best cut-off point of the pretreated scar volume for predicting a 50% scar reduction was 1.5 cc. Pretreated scar values of less than 1.5 cc correlated with successful scar reduction (sensitivity = 100%, specificity = 57%). The ratio of red (mature) collagen fibers to green (young) collagen fibers obtained by the Picrosirius red color spectral analysis and the subsequent polarization microscopy revealed the following red to green ratios: in the pretreated scar = 1.4 ± 0.15; at 1 month post-treatment = 1.14 ± 0.15; at 3 months post-treatment = 1.06 ± 0.2. All differences were statistically significant (p<0.001).

The orientation index was significantly higher in the post-treated scar (2.06 ± 0.7) as compared with the untreated keloid (1.40 ± 0.2, p=0.044). Hence, the architectural pattern of the collagen is more organized in the treated scar, i.e., the parallel organization of the collagen fibers in the treated scar is similar to that in the normal dermis, in contrast to the disorientation of the collagenous network viewed in the non-treated scar.
Results of the second study revealed the following:
The time required to achieve complete freezing of the auricular keloids was between 5 to 30 minutes, depending on the volume of the scar treated.

A significant reduction in objective parameters and alleviation of the subjective complaints were achieved. The average volume of the keloids before treatment being 2.89 ± 0.69 cm$^3$ (range 1–6 cm$^3$) was significantly reduced to 1.17 ± 0.46 cm$^3$ (range 0–4 cm$^3$) 6 months after a single session of intralesional cryosurgery, which represents a volume reduction of 67.4 ± 23% (p<0.005). In addition, the redness score was reduced from 2.90 ± 0.10 before treatment to 0.80 ± 0.32 6 months after cryosurgery (p<0.007), the hardness score from 2.90 ± 0.10 to 0.50 ± 0.22 (p<0.004) and the elevation score from 3.00 ± 0.00 before treatment to 1.00 ± 0.10 6 months after cryosurgery (p<0.006). No scar recurrence or worsening was registered during the 18-month follow-up period.

The patients mentioned a significant reduction of their subjective complaints a few days after the treatment, which persisted during the follow-up period. The itching score before treatment was 2.50 ± 0.34 compared with 1.19 ± 0.37 6 months after cryosurgery (p<0.023). The pain score was 2.00 ± 0.44 before treatment and 0.30 ± 0.21 6 months after cryosurgery (p<0.016), and the tenderness score was 2.30 ± 0.33 before treatment and 0.40 ± 0.22 6 months after cryosurgery (p<0.007).

The thermal history of the isolated intralesional cryoprobe demonstrated a fast cooling rate (200°C/min). The end temperature was shown to be -196°C, which was achieved after 60 seconds and remained at this low level for another 120 seconds (hold time). The thawing rate was equally fast, i.e. the temperature returned from approximately -200°C to almost 0°C (200°C/min) after 60 seconds. The contact cryoprobe also exhibited a fast cooling rate (160°C/min), i.e. the probe temperature was -136°C after 60 seconds, which remained constant until 180 seconds. The thawing rate, however, was very slow (40°C/min), i.e. the probe temperature was -35°C at 420 seconds.

Ex-vivo studies revealed a completely different thermal behavior. The intralesional cryoprobe showed a much slower cooling rate (20°C/min) with an end temperature of -30°C. However, the thawing rate was faster (35°C/min). The contact probe showed fast cooling and thawing rates (80°C/min) with an end temperature of -100°C and without a constant hold time.
The results of the **third study** demonstrated the following findings:

The comparison of the surface thermal histories of the two cryosurgery techniques revealed a significant difference. Intralesional cryosurgery had significant slower cooling and thawing rates (6.09 ± 4.56 and 13.47 ± 9.04°C/min, respectively) when compared with the cooling and thawing rates of the contact method (54.52 ± 32.17 and 89.00 ± 86.42°C/min respectively) (p<0.000001). The end temperature of the contact technique was significantly cooler when compared with that of the intralesional method (-46.77 ± 14.74 and -15.55 ± 6.77°C, respectively) (p<0.000001). The hold time of intralesional cryosurgery was significantly longer compared with the hold time of the contact method (82.67 ± 138.03 and 16.86 ± 23.49 sec, respectively) (p<0.059). Both groups of the treated HKS were examined 6 months following the cryosurgery treatments. Twelve patients with 12 HKS treated by the contact method (80%) and 14 patients with 22 HKS treated by the intralesional technique (93.3%) were evaluated for pigmentation changes following a single freezing cycle. Hypopigmentation grading scores were evaluated. The results revealed a significant difference in skin pigmentation between the two cryosurgical methods. In 91.7% of the HSK treated by the contact technique, a significant hypopigmentation (score 1 and 2) was noticed while the skin surface of the HKS treated by the intralesional method exhibited no significant hypopigmentation, i.e. 0% (score 1 and 2) (p< 0.0001).

**Conclusions**

This simple-to-operate intralesional cryoprobe technique can be applied to every scar shape and contour with a sufficient volume and may be added to the armamentarium of methods that treat hypertrophic scars keloids. There is no need for control of freezing time since the treatment ends when the lesion becomes clinically completely frozen.

The thermal history of the skin surface during the intralesional cryosurgery technique may provide a better survival environment for the melanocytes compared with that of the contact method, thus producing lower permanent hypopigmentation and disfigurement.

The histomorphometric analysis demonstrated rejuvenation of the treated scars, i.e., parallelization, and a more organized architecture of the collagen fibers when compared to the pretreated scars, which might contribute to the low recurrence of the treated HSK.
Furthermore, the major advantage of the intralesional cryoprobe is the ability to destroy the deeply localized target tissue of the core of the HSK with minimal effect on the superficial skin layers. This may be of paramount importance in the clinical application of cryosurgery, not only in the treatment of keloids, but also of other localized deep skin lesions and tumors. In addition, the marked efficacy of a single intralesional cryosurgery session presented is another major advantage in comparison to the repeated sessions of standard contact cryosurgery required. From a technical point of view, the presented intralesional cryoprobe technique is safe to use, consumes less cryofluid when compared with the open cryosystems, necessitates a short learning curve and reduced postoperative care of the wound, and can easily be added to any pre-existing cryosurgical unit.
References


Har-Shai Y., Dujovny E., Rohde E., Zouboulis C.C., Effect of skin surface temperature on skin pigmentation during contact and intralesional cryosurgery of keloids. Accepted for publication, The Journal of the European Academy of Dermatology and Venereology, 2006.
Figures

Left: A preoperative view of a 4-year-old keloid on the left nape following a neurosurgical operation. Right: 18 months after a single intralesional cryosurgery, the keloid was flattened with no recurrence or hypopigmentation.
**Upper left:** A preoperative view of a 5-year-old keloid following excision of a nevus on the anterior chest, which was treated unsuccessfully by silicone ointments and sheeting, and intralesional corticosteroid injections. **Upper right:** Intra-operative intralesional cryosurgery of the keloid. **Lower left:** 7 days following cryosurgery. A blister and epidermolysis is noticed. **Lower right:** 2.5 years after a single intralesional cryosurgery, the keloid is flattened with no recurrence or significant hypopigmentation.

**Chest**

![Images of preoperative, intra-operative, and postoperative views of a keloid on the chest following cryosurgery.]