Pain evaluation and control during and following the treatment of hypertrophic scars and keloids by contact and intralesional cryosurgery – a preliminary study

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Abstract

Background Intralesional cryosurgery effectively treats hypertrophic scars and keloids (HSK), but pain experienced by the patient during treatment can limit the application of cryosurgery.

Objectives To characterize the pain response during cryosurgical treatment of HSK, and to evaluate the pain experienced during contact and intralesional cryosurgery that employs a pain-control protocol.

Methods Twenty-nine patients (17 women, 12 men) aged 17 years and older (mean ages 31.9 ± 12.5 and 38.9 ± 18.6 years, respectively, P = 0.24), who were treated for a total of 36 HSKs by intralesional (n = 20; 22 cryotreatments) or contact (n = 9; 14 cryotreatments) cryosurgery were evaluated. The pain-control protocol involved oral pain-relief tablets (Dipyrone) and translesional local anaesthesia with Bupivacaine hydrochloride 0.5%. Pain evaluation according to the Visual Analogue Scale (VAS) (0–10 cm) was compared between the two groups at three time points: during cryosurgery, immediately after it, and 4 h later. Scores £ 3 cm were considered to define the ‘zone of analgesic success’. These results were compared with control data (contact cryosurgery without a pain-control protocol; n = 56).

Results Pain in the intralesional group was significantly lower than that in the contact group during and immediately after cryotreatment. During: mean VAS = 1.68 ± 2.21 vs. 5.07 ± 4.01 cm; median VAS = 0 vs. 5.5 cm, respectively; P < 0.0001. Immediately after: mean VAS = 1.22 ± 1.77 vs. 5.38 ± 3.81 cm; median VAS = 0 vs. 6.0 cm, respectively; P = 0.001. The control group had more pain during treatment (mean VAS = 5.34 ± 2.31, median = 6.0) and 4 h later (mean = 3.79 ± 2.35, median = 4.0) than the intralesional group (P < 0.0001 and P = 0.988, respectively). The pain level in the control group during the cryotreatment did not differ from that in the contact group (P = 0.988). In the intralesional, contact and control groups analgesic success (VAS £ 3 cm) was achieved in 77.3%, 35.7% and 33.9%, respectively, of cases (P = 0.002) during cryotreatment, and in 54.5%, 42.9% and 33.9%, respectively, of cases 4 h after treatment (P = 0.24).

Conclusions The pain-control protocol significantly reduced pain severity to tolerable levels (VAS £ 3 cm) during and following intralesional and contact cryosurgery. Intralesional cryosurgery caused the least pain during and immediately after treatment.

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Conflicts of interest

The author Y.H. has a financial interest in the intralesional cryosurgery technology.

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Introduction

Hypertrophic scars and keloids (HSK) result from an abnormal response of connective tissue following skin trauma. They occur among people with genetic predisposition, but the aetiology for formation of HSK still remains unclear; they occur with equal frequency in men and women, most often between 10 and 30 years of age. Youngsters are more prone to trauma and exhibit higher skin tensile strength and faster collagen synthesis than older people.

Patients suffering from HSK seek medical help mainly for cosmetic reasons, but also because of their impaired quality of life.
and the distortion of body image that can interfere with social interactions. Moreover, symptoms of tenderness, itching, pain, discomfort and burning sensations require medical intervention.

Since publication of the modern description of keloids by Albert, many therapeutic techniques have been offered; they include corticosteroid injections, pressure therapy, silicone occlusive sheeting, cryosurgery, retinoids, interferon injections, 5-FU, colchicine, calcium-channel blockers, laser, chemotherapy and radiation treatments, and surgical excision, as well as combinations of these treatment modes.

In 1982, Shepherd and Dawber were the first to introduce contact cryosurgery for treatment of HSK. Since then, cryosurgery has become an evidence-based technique that has proved to be safe and effective for treatment of HSK. Currently, contact cryosurgery is the common cryosurgical method, but recently the innovative new technology of intralesional cryosurgery was described by Har-Shai et al. This approach results in enhanced freezing of the core of the HSK, with minimal damage to the skin surface. In the ear, upper back and shoulders and chest areas, average HSK-volume reductions of 67%, 60% and 50%, respectively, following a single intralesional cryosurgery session were documented.

In 1986, the International Association for the Study of Pain (IASP), described pain as an ‘unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.’ According to Rosilene et al., the application of liquid nitrogen to the skin induces local inflammation and elicits release of inflammatory mediators that cause pain.

Gupta et al. demonstrated that the severity of pain during skin cryosurgery based on the spray technique ranged between 2.91 and 5.59 cm on the VAS scale, whereas pain scores in the group that had been topically pretreated with eutectic lidocaine/prilocaine cream 5% (EMLA) were reduced to between 2.25 and 4.7 cm.

Skin cryosurgery inevitably entails pain. Therefore, pain experienced by the patient could limit the wide-ranging application of this effective technology, and it is of great importance that the procedure be as painless, pleasant and comfortable as possible, for the patient.

Aims of the study
The aims were: firstly, to characterize the pain responses during and after contact cryosurgery treatment of HSK, in patients who did not receive treatment for procedure-related pain (control); secondly, to characterize the pain responses during and after contact and intralesional cryosurgery treatment of HSK, in patients who received treatment for procedure-related pain; and thirdly, to compare the results obtained with the two respective groups.

Materials and methods
This study has been conducted at the Department of Plastic Surgery, Linn Medical Center, Haifa over a 4-year period (from 2005 to 2009) and had been approved by the institutional ethical committee. The enrolled patients or their legal guardians had signed consent forms.

Patients were randomly allocated to the intralesional and contact groups, and the size (n) of the studied groups was determined by the statistician to facilitate power analyses.

Criteria for exclusion from this study were: active infection, malignancy, immunodeficiency conditions, diseases that react adversely to cold, wound-healing abnormalities, proximity of vital organs to treatment sites, blood dyscrasia and sensory disturbances, e.g. diabetes, alcoholism, etc. All the treated HSK had existed for more than 6 months.

Pain was evaluated according to the Visual Analogue Scale (VAS) during, immediately after and 4 h after cryosurgery. The VAS is a psychometric scale that depicts subjective characteristics, e.g. pain perception, as locations on a continuous line between two end points: 0 cm corresponds to no pain (0) and 10 cm to unbearable pain. It has been stated by Mantha et al. and Zaslansky et al. that scores of £5 represent ‘mild’ pain and can be regarded as the ‘zone of analgesic success’. Therefore, the aim of this study was to obtain such scores (£5) during and following cryotreatment. The patients did not undergo pretreatment training with respect to the VAS.

A control group of 56 Caucasian patients (28 women and 28 men), older than 17 years, who had suffered from HSK for more than 6 months, was designated to characterize the pain response without use of a pain-control protocol. These patients were treated by contact cryosurgery; they had been evaluated prior to the design and employment of the pain-control protocol, therefore, they were assessed at only two time points: during and 4 h after the cryotreatment.

The second studied group comprised 29 Caucasian patients, older than 17 years (men/women ratio 0.70), who had suffered from HSK for more than 6 months. They underwent a total of 36 separate cryosurgery procedures (contact, n = 14; intralesional, n = 22) which included a pain-control protocol. The aetiologies of their HSK scars were: piercing, (men/women) 14/29; acne, 7/29; trauma, 4/29; surgery, 3/29 and burns, 1/29.

For those patients who underwent more than one procedure in this study, the time interval between cryo treatments was more than 6 months; therefore, the second treatment was regarded as a primary cryo session.

The pain-control protocol (Fig. 1) comprised intake of a 500-mg tablet of Dipyrone (Metamizole) (Teva Pharmaceutical Industries Ltd. Petah Tikva, Israel) 1 h prior to treatment. Dipyrone (Metamizole) is a non-steroidal anti-inflammatory drug (NSAID) oral pain-relief tablet with pain-relieving, antipyretic and anti-inflammatory properties; it exhibits proven efficacy after day surgery and minor surgery. The tablet was followed by a translesional local anaesthetic injection of bupivacaine hydrochloride 0.5% (Kamacaine; Kamada, Beit Kama, Israel) via a 23G hypodermal needle that was inserted perpendicularly to and through the entire
thickness of the scar into the loose subcutaneous fat tissue (Fig. 2). This approach enables the anaesthetic solution to be easily infiltrated into the underlying HSK tissue with no resistance and with minimal pain. Furthermore, the translesional approach entails no injury to the surrounding normal skin, and therefore avoids possible development of new abnormal scarring.

The cryotreatment was initiated about 10 min after the injection of local anaesthetic to enable the latter to act; immediately after the treatment another pain-reliever tablet was taken. Thereafter, the patient was instructed to take extra pain-reliever tablets every 4 h, according to the pain level. All cryotreatments were administered by the same physician (Y.H.). Each patient was asked by the assistant physician (O.M.) and the accompanying licensed nurse (I.G.) to evaluate the pain during – usually at the middle of – the procedure, i.e. after 30 s of the contact, by which time approximately half of the scar was frozen, and again immediately after treatment. Four hours after the procedure the patient was contacted by telephone to ascertain their pain score, after which there was no further follow-up regarding Dipyroline use.

For each patient in this group, gender and HSK location were documented (Table 2). To compare the pain sensation intensities between men and women and between HSK locations, during, immediately after and 4 h after cryosurgery, the two groups – intrallesional and contact cryosurgery – were combined.

The duration of the contact/intrallesional cryotreatment was measured in minutes.

**Cryosurgery treatment**

**Intrallesional cryosurgery method** The scar is disinfected and the underlying subcutaneous tissue beneath it is locally anaesthetized by translesional administration of Bupivacaine 0.5% (Fig. 2). Thereafter, a sterile cryoprobe (CryoShape; Etgar Group International, Kfar Saba, Israel) is forced into the core of the scar along its long axis, which is parallel to the skin surface.15–20 The proximal part of the probe is connected to a cryo gun (Brymill Cryogenic Systems, Ellington, CT, USA) filled with liquid nitrogen. Activation of the cryo gun trigger drives cryogenic liquid nitrogen through the cryo needle, thereby freezing the abutting scar. Upon complete freezing of the scar, which is evident clinically, and regardless of the duration of the cryosurgery process, i.e. without necessity to record the time, the freezing process is stopped and the cryo needle is withdrawn.

**Contact cryosurgery method** Following translesional local anaesthesia (as described above), a 1-cm-diameter metallic contact cryoprobe (Brymill Cryogenic Systems) connected to the cryo gun is applied to the HSK surface6,17 and activated. During treatment,
Ice forms on the HSK surface and spreads radially. Upon complete freezing of the scar, which is evident clinically, and regardless of the duration of the cryosurgery process, the freezing process is stopped and the contact Cryoprobe is removed from the scar surface.

Statistical methods

Sample size The data of 56 patients in the control group, who were treated for HSK during the last 3 years, have been collected retrospectively.

To evaluate the pain level which has been experienced by the patients during contact and intralesional cryosurgery, employing a pain-control protocol, and to compare it with the pain experienced by the control group, about 50 consecutive patients of all ages were alternately allocated for the two studied groups during a period of 1 year.

After excluding the patients younger than 17 years, 20 patients in the intralesional cryosurgery group have contributed 22 HSK whereas, nine patients in the contact group have contributed 14 HSK.

Given a = 0.02 (Multiple Comparison) - these samples size, in which the VAS scores of ≤3 have been considered as ‘Zone of Analgesic Success’, allowed to detect a statistically significant difference in pain level of about 40% among the control group and the intralesional and contact groups, as well as between the studied groups, with a power between 64% and 80%.

Statistical analysis Data were analysed with the SPSS 15 statistical package (SPSS, Chicago, IL, USA).

The correlations between the three treatment groups (control, contact and intralesional) and VAS pain evaluation, categorized on two levels (≤3 and >3), were subjected to the chi-squared test.

The Kruskal–Wallis test was employed to compare the VAS ratings of pain (as a continuous variable), as perceived by the three respective treatment groups, and as perceived by the respective HSK-location groups.

For multiple comparisons between two independent groups, the Mann–Whitney U-test was applied.

The age difference between the two study groups was subjected to Student’s t-test, and the gender distribution between the two groups was subjected to the Fisher exact test. The Friedman test was used to analyse the variations of pain intensity over time.

Pearson correlation coefficients were calculated to examine the correlations between duration of the procedure and pain levels perceived by the intralesional group at the three time points.

A Box-plot was employed to depict the median, interquartile range and outliers of the pain intensity over time in each of the groups.

Table 1 Comparison among the pain levels of the control, contact and intralesional cryosurgery groups, as registered on the Visual Analogue Scale (VAS) at the three time points. The pain was analysed as a continuous variable [mean (SD), median] and a categorical variable [n(%)]. (NA – not available)

<table>
<thead>
<tr>
<th></th>
<th>Control, n = 56</th>
<th>Contact, n = 14</th>
<th>Intralesional, n = 22</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>19 (33.9)</td>
<td>5 (35.7)</td>
<td>17 (77.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt;3</td>
<td>37 (66.1)</td>
<td>9 (64.3)</td>
<td>5 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Pain during treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.34 (2.31)</td>
<td>5.07 (4.01)</td>
<td>1.68 (2.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median</td>
<td>6.0*</td>
<td>5.5**</td>
<td>0.5***</td>
<td></td>
</tr>
<tr>
<td>Pain immediately after treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>NA</td>
<td>4 (30.8)</td>
<td>18 (81.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>&gt;3</td>
<td>9 (69.2)</td>
<td>4 (18.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain immediately after treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.38 (3.81)</td>
<td>5.29 (3.85)</td>
<td>3.45 (2.65)</td>
<td>0.289</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
<td>6.5</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

Multiple comparison: *Control vs. Intralesional P < 0.0001, **Control vs. Contact P = 0.988, ***Contact vs. Intralesional P = 0.011.
†Pain VAS measurement categorized by two levels (≤3; >3).

Table 2 Comparison between pain perceptions of men and women and between different locations, at the three time points (with the pain-control protocol in use)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Location</th>
<th>Male</th>
<th>Female</th>
<th>P-value</th>
<th>Ear</th>
<th>Sternal</th>
<th>Miscellaneous</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during treatment</td>
<td>4.29 (3.36)</td>
<td>4.00 (3.07)</td>
<td>1.00</td>
<td>0.102</td>
<td>1.13 (2.26)</td>
<td>0.0</td>
<td>5 (3.62)</td>
<td>4.5***</td>
</tr>
<tr>
<td>Pain immediately after treatment</td>
<td>3.64 (3.59)</td>
<td>3.00 (3.14)</td>
<td>1.00</td>
<td>0.186</td>
<td>0.93 (1.67)</td>
<td>0.1</td>
<td>4.83 (3.71)</td>
<td>4.5***</td>
</tr>
<tr>
<td>Pain 4 h after Treatment</td>
<td>4.36 (3.43)</td>
<td>4.00 (3.2)</td>
<td>3.5</td>
<td>0.835</td>
<td>3.33 (2.74)</td>
<td>3</td>
<td>4.83 (3.22)</td>
<td>4.5***</td>
</tr>
</tbody>
</table>

Multiple comparison: *Auricle vs. Sternal P = 0.003, **Auricle vs. Miscellaneous P = 0.019, ***Auricle vs. Miscellaneous P = 0.076, ****Sternal vs. Miscellaneous P > 0.3.

VAS, Visual Analogue Scale.
All $P$-values were two-sided, and statistical significance was defined as $P < 0.05$.

**Results**

The patients’ mean ages in the intrallesional and contact cryosurgery groups were 31.9 ± 12.5 and 38.9 ± 18.6 years, respectively. The intrallesional and contact groups comprised 45% ($n = 9$) men and 55% ($n = 11$) women, and 33.3% men ($n = 3$) and 66.7% women ($n = 6$), respectively; $P = 0.6$.

The control group comprised 56 Caucasian patients (28 women and 28 men), older than 17 years.

**Effect of treatment**

Treatment duration in the contact cryosurgery group was up to 1 min; that in the intrallesional group ranged from 4 to 150 min, with an average of 26.5 min. No correlation was found between the treatment duration and the pain level at the three time points, for which $P = 0.45, 0.26$ and 0.27, respectively.

There were significant differences in pain perception among the control, contact and intrallesional groups at all time points.

During treatment, VAS scores $>3$ cm were found in 66.1% of control patients, compared with 64.3% in the contact group and 22.7% in the intrallesional group; $P = 0.002$. Four hours after cryosurgery the corresponding percentages were 66.1%, 57.15% and 45.5%, respectively; $P = 0.242$ (Table 1).

During cryosurgery there were significant ($P = 0.011$) differences in VAS scores between the contact and intrallesional groups: in the contact group the mean score was 5.07 ± 4.01, with a median of 5.5; in the intrallesional group the mean was 1.68 ± 2.21, and the median 0.5 (Table 1, Fig. 3). Also immediately after cryosurgery there were significant ($P = 0.001$) differences between the intrallesional and the contact groups: mean, 1.22 ± 1.77, median 0.0; and mean, 5.38 ± 3.81, median, 6.0, respectively (Table 1, Fig. 3). However, at 4 h after cryosurgery no significant difference ($P = 0.289$) in pain perception was found among the intrallesional, contact and control groups (Table 1).

In the intrallesional group significant ($P = 0.015$) differences in pain perception were found among the three time points, but in the contact group no such differences were found ($P = 0.9$) (Fig. 3).

**Effect of treatment location**

In the intrallesional cryosurgery group the treatment locations were: ear 59.1%, sternum 22.7% and miscellaneous (other body areas) 18.2%. In the contact group they were: ear 15.4%, sternum 53.3% and miscellaneous 30.8%.

No difference in VAS scores was found between sternum and miscellaneous, therefore these two locations were combined for comparison between the intrallesional and contact methods regarding pain levels.

No significant difference ($P > 0.1$) in pain perception was found between men and women (Table 2). However, significant differences were found between different body locations during ($P = 0.004$) and immediately after ($P = 0.007$) cryosurgery. In particular, when the ear and the sternum were compared during and immediately after cryosurgery ($P = 0.003$), and the ear and miscellaneous locations were compared during the treatment ($P = 0.019$), the ear was found to be the least painful location (Table 2). Although, no statistically significant differences ($P = 0.24$) were found 4 h after cryosurgery, the findings for the ear and the sternum showed the same trend (Table 2).

Although the location distributions differed between the intrallesional and contact groups ($P = 0.053$), and the pain perception in the ear was significantly less than that in the other two locations, the pain level was significantly dependent on the cryotreatment method (intrallesional vs. contact), and not only on the treatment location (Table 3).

**Discussion**

This pilot study yielded preliminary findings from a small group of patients. Patients treated by intrallesional cryosurgery coupled with a pain-reduction protocol reported less pain during and immediately after treatment than those treated by the current ‘gold standard’ (contact cryosurgery) method, and than the controls who received no treatment for pain. Four hours later, patients in the three groups reported moderate to severe pain. The small numbers of patients in the intrallesional and contact groups limit interpretation of the study; thus further work is warranted.

Application of liquid nitrogen to the skin elicits two inflammatory reactions characterized partially by pain. The first is the inflamma-
matory pain caused by mediators such as kinins and substance C, which stimulate the free terminal of the neural cells (C fibres) to conduct a direct and rapid pain signal to the brain.21 The second is a mechanical nociceptor hypersensitivity which is elicited by the cytokines that are released by defence cells and which may intensify the pain via the actions of arachidonic acid/cyclo-oxgenase products, sympathomimetic amines, TNF-cytokines that are released by defence cells and which may intensify a mechanical nociceptor hypersensitivity which is elicited by the pain comparison (VAS), mean (SD) median VAS, Visual Analogue Scale.

Table 3 Comparison between pain perceptions of the intraleisional and contact cryosurgery groups, within the various locations, at the three time points (with the pain-control protocol in use)

<table>
<thead>
<tr>
<th>Location treatment</th>
<th>Contact, n = 3</th>
<th>Intraleisional, n = 13</th>
<th>P-value</th>
<th>Contact, n = 11</th>
<th>Intraleisional, n = 9</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain during treatment</td>
<td>0.33 (0.6) 0</td>
<td>1.23 (2.4) 0</td>
<td>0.9</td>
<td>6.36 (3.5) 8</td>
<td>2.33 (1.8) 2</td>
<td>0.012</td>
</tr>
<tr>
<td>Pain immediately after treatment</td>
<td>0.5 (0.7) 0.5</td>
<td>1 (1.8) 0</td>
<td>0.9</td>
<td>6.27 (3.4) 8</td>
<td>1.55 (1.8) 1</td>
<td>0.006</td>
</tr>
<tr>
<td>Pain 4 h after treatment</td>
<td>1.33 (1.5) 1</td>
<td>3.77 (2.7) 3</td>
<td>0.11</td>
<td>6.36 (3.6) 7</td>
<td>3 (2.7) 2</td>
<td>0.038</td>
</tr>
</tbody>
</table>

VAS, Visual Analogue Scale.

Dipyrone (Metamizole) is a NSAID, which was first synthesized in 1920 in Germany, and was launched there in 1922; it has pain-relieving, antipyretic and anti-inflammatory properties, and has proved efficacious following day surgery and minor surgery. The NSAIDs reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2.26

It has been demonstrated experimentally by Rezende et al.27 that Dipyrone is not a ‘classical’ NSAID, but rather an anomalous NSAID, since its effect appears to be central and not peripheral,28 its mode of action is independent of the endogenous opioid system, therefore its anti-inflammatory effect is weak.

The pharmacokinetics of Dipyrone are characterized by rapid hydrolysis to the active moiety 4-methyl-amino-antipyrine (MAA), which has 85% bioavailability after oral administration in tablet form, and that achieves maximal systemic concentrations within a short time ($t_{max}$ of 1.2–2.0 h). The MAA is further metabolized to 4-formyl-amino-antipyrine, with a mean elimination half-life ($t_{1/2}$) of 2.6–3.5 h.29

Since Dipyrone does not accumulate in the tissue, it should be free of the adverse gastrointestinal and renal effects associated with anti-inflammatory drugs. Although Dipyrone is the most popular non-opioid, first-line analgesic in many countries, it has been banned in others, e.g. USA, UK and Sweden, because of its association with potentially life-threatening blood dyscrasias such as agranulocytosis.30 Currently, Dipyrone is available in Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Switzerland, South Africa, Latin America, Russia, Israel and India.26

It has been documented that a single oral dose (500 mg) of Dipyrone achieved a mean of 73% pain relief over 4–6 h in patients with moderate to severe postoperative pain.21 Thus, administration of Dipyrone (with its $t_{1/2}$ of 2.6–3.5 h) 1 h before treatment, together with local-anesthesia injections of bupivacaine hydrochloride 0.5% (with $t_{1/2}$ of 2.7 h) would provide pain relief for up to 4 h during and following cryosurgery.

In addition, a single dose of Dipyrone was shown to exhibit similar efficacy to Ibuprofen 400 mg,26 so that in those countries in which Dipyrone is banned Ibuprofen could be an effective substitute. However, on the other hand, it would be necessary to administer the latter in doses of at least 1200 mg/day, on the day of treatment and the following 1 or 2 days.

Lee et al.32 reported that pain is a common presentation in keloids and is associated with abnormalities in small-nerve-fibre function, which suggests a small-nerve-fibre neuropathy. Furthermore, 77% of HSK patients were very sensitive to mechanical stimuli at the centre of the keloid. Therefore, the intake of an NSAID pain-relief tablet 1 h prior to treatment is intended to relieve the patient of the pre-existing HSK pain and of his/her fear of the needling involved in local anaesthesia.

Topically applied eutectic lidocaine/prilocaine cream (EMLA) 5%22 also might be used to anaesthetize the HSK skin before needle insertion for local anaesthesia, but the efficacy of EMLA on scar tissue is not certain.

Although the time duration of intraleisional cryosurgery in this study ranged from 5 to 150 min, the average treatment time was 26.5 min. However, no correlation was found between the duration of the cryosurgery and the pain levels at the three monitored time points. In fact, the patient whose treatment took 150 min (the longest intraleisional treatment to date) experienced no pain throughout the procedure.

Injection of bupivacaine hydrochloride 0.5% ensures relatively rapid onset of analgesia and the effect is long-acting. In addition, analgesia persists for some time after the return of sensation, thereby reducing the subsequent need for strong analgesics and enabling use of only a pain-relief tablet.

The half-life of bupivacaine hydrochloride 0.5% in adults is 2.7 h, which might account for the relative increase of pain perception in the intraleisional and contact groups after 4 h. Another interpretation of this finding is that the patients did not take the pain-relief tablets as suggested to them. This outcome possibly could have been improved if patients had taken the prescribed additional medication.
Another explanation for the differences in pain perception between the intralesional and the contact cryosurgery groups springs from the fact that most of the sensory nerve endings or nociceptors are located close to the epidermis \(^{32,33}\) and are affected by the \(-50^\circ C\) temperature that prevails during contact cryotreatment.\(^{16,17}\) In contrast, with the intralesional cryosurgery technique, the zone of the lowest temperature does not touch the epidermis,\(^{16}\) which is exposed to a temperature of only \(-16^\circ C\),\(^{16,17}\) so that pain inflammatory responses are lesser than those associated with the contact method.

It has been found that the ear was the least painful cryosurgery location, both during and immediately after the procedure. This might be associated with a similar effect associated with sham acupuncture of the ear, i.e. needling of non-acupuncture points, which is based on the fact that the cutaneous penetration of the needles causes a physiological reaction, i.e. triggering of neural pathways that results in diffuse noxious inhibitory control.\(^{34}\) In this study, the local-anaesthesia needling as well as the intralesional insertion of the cryoprobe, also might have stimulated neural pathways, which might produce an analgesic effect.\(^{35}\) Therefore, this hypothetical effect of the cryosurgery needling might have an additive effect on pain control at the ear during and after the intralesional cryotreatment. It should be stressed that the pain level was found to be significantly dependent on the cryotreatment method (intralesional vs. contact). Therefore, employment of the intralesional approach will be less painful than the contact technique in all body locations.

In a recent article, Ogawa\(^{36}\) discussed the current protocols for treatment and prevention of HSK, and categorized induction of severe pain in cryosurgery as a drawback of this technique. However, the pain scores recorded by patients in this study provide subjective evidence that such pain can be effectively managed and reduced by this proposed pain-control protocol.

In conclusion, this study has demonstrated that the pain-control protocol significantly reduced pain severity to tolerable levels (VAS ≤3 cm) during and following intralesional and contact cryosurgery. Intralesional cryosurgery caused less pain during and immediately after treatment than that experienced with the contact technique.

References
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