Original Article

The Efficacy of Skin Cooling for Pain Relief during Intralesional Steroid Injection for Keloid Treatment: A Randomized Cross-Over Study

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Background: An intralesional corticosteroid injection is one of the most effective and popular treatment for keloid, however severe pain during injection is the most complaint.

Objective: To evaluate if pre-treatment skin cooling can reduce the pain during steroid injection.

Materials and Methods: A randomized cross-over study was conducted between September 2015 and October 2016. This study received ethical approval ID035904 No. MURA2016/152. Forty-four subjects with keloid that needed intralesional steroid injection were divided into three pre-treatment groups, no treatment, skin cooling with ice pack, and skin applying with a mixture of lidocaine 2.5% and prilocaine 2.5% (EMLA®), in random order. Pain intensity was measured by using 100-mm visual analogue scale (VAS). The satisfaction levels were assessed with orderly interval rating scale from 1 to 5. Repeated-measure analysis of variance (ANOVA) and Bonferroni pairwise comparison were used for data analyses.

Results: The mean VAS score at the time of needle puncturing into the skin and during steroid infiltration was statistically significant lower in skin cooling compared to no treatment group ($p<0.001$) and EMLA group ($p<0.05$). The satisfaction level was also statistically significant higher in skin cooling compared to no treatment group ($p<0.001$) and EMLA group ($p<0.001$). Thirty-seven patients (84%) selected skin cooling method as the most favorable pre-anesthetic method for intralesional steroid injection.

Conclusion: Skin cooling with ice before intralesional steroid injection of keloid effectively reduces pain and patients are also satisfied.

Keyword: Keloid, Corticosteroid, Pre-treatment, pain, skin cooling

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Keloid is an abnormal wound healing process resulting in aberrant collagen formation attributing to pruritus, pain, and unaesthetic appearance. The etiology and pathophysiology of keloid formation remain unknown. Many treatment modalities have been applied, such as intralesional corticosteroid injection, surgical excision, silicone gel sheeting, pressure therapy, and laser, but none can effectively cure the disease.

The intralesional corticosteroid injection, first reported in 1961[1], is still one of the most effective and widely used monotherapy or adjuvant modality to treat keloid. However, there are some side effects of corticosteroid including skin atrophy, telangiectasia, and dyspigmentation. Moreover, the severe pain during injection causes poor compliance of the patients.

To reduce the pain during injection, many pretreatment protocols are applied such as mixing corticosteroid with lidocaine, lidocaine tape, Eutectic Mixture of Local Anesthesia (EMLA), and skin cooling. By comparing to the other methods, skin cooling is the simplest technique. It can be easily performed by iced packing. Skin cooling has been used to decrease skin sensation in various procedures such as physical therapy and laser treatment. The efficacy of skin cooling in pain reduction during intralesional corticosteroid injection for keloid and hypertrophic scar treatment has not been reported. Therefore, the present study aimed to explore the efficacy of skin cooling to reduce pain during intralesional corticosteroid injection for keloid management.

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Table 1. Show how to randomize the patients into 6 groups in order to get pretreatment before triamcinolone injection

Group	First visit	Second visit	Third visit
1	No Treatment	EMLA	Skin cooling
2	No Treatment	Skin cooling	EMLA
3	EMLA	No Treatment	Skin cooling
4	EMLA	Skin cooling	No treatment
5	Skin cooling	No Treatment	EMLA
6	Skin cooling	EMLA	No treatment

EMLA=Eutectic Mixture of Local Anesthesia

Materials and Methods

The present study was a randomized crossover clinical trial conducted in Ramathibodi Hospital, Mahidol University, between September 2015 and October 2016. The study was approved by the Ethical Board Review ID035904 No. MURA2016/152 of Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, and followed the ethical standards of the Declaration of Helsinki. Participants were 18 years or older with keloid that required intralesional corticosteroid injection for at least three visits. The exclusion criteria were participants who were contraindicated for the corticosteroid administration, allergic to corticosteroid and EMLA, and having intralesional corticosteroid injection within three months.

All participants were informed and accepted the protocol of the treatment. The patient's demographic data were collected, and they were randomized into six groups with box randomization (Table 1). Regarding to the nature of pre-treatment protocol, the concealment of the study was not possible.

In each group, all the patients received the three modalities of pretreatment before corticosteroid injection in previously randomized orders including the controlled group without pretreatment, skin cooling with ice pack, and EMLA groups. Skin cooling was done by application of an ice pack directly on the keloid for three minutes. The EMLA group was applied EMLA cream on keloid and covered with film for 60 minutes prior to injection for maximum effect.

Triamcinolone acetonide (TA) (10-mg/mL, SHINCORT INJ®) was administered at three to five weeks interval. The dosage of steroid was approximated 1 mL per 1 $cm^{(2)}$ of keloid surface area and the speed of free hand injection was about 0.1 mL per 10 to 15 seconds.

Pain intensity of the first injection of each visit was assessed three time, pain when needle piercing into the scar (T1), pain during infiltration (T2), and pain after one hour of the infiltration (T3), by using 100-mm visual analogue scale (VAS). The level of satisfactions was categorized into five levels, very dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied, and very satisfied, respectively. At the last visit, all participants were asked to choose the most favorite pretreatment for their further steroid injections. All patients were examined and treated by a single physician.

Statistical analysis

The sample size was 50 participants calculated regarding to the crossover design with accepted 5% type 1 and 10% type 2 error and included for 20% dropout rate. The VAS data were analyzed with the Repeated Measurement ANOVA and pairwise comparison by Bonferroni adjustment. The Satisfaction level for each modality were analyzed with the Repeated Measurement ANOVA and pairwise comparison by Bonferroni adjustment. A p-value of less than 0.05 was indicated significance. Statistical analyses were carried out in PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were applied on categorical data.

Results

Fifty patients were enrolled in the present study. Six patients dropped out from the study because five patients were loss of follow up and one case of the keloid was completely resolved after two sessions of steroid. Among 44 patients, there were 41 (93.2%) females with mean age was 39.9 years and a range of 18 to 76 years. Other demographic data are presented in Table 2.

The mean VAS score immediately at the time that the needle piercing into the skin (T1) were 42.6±3.7, 10.9±2.6, and 23.4±3.5 for control group, skin cooling-method group, and EMLA-method group, respectively (Table 3). The mean VAS score at T1 for the skin cooling method was statistically significantly lower than the control method ($p<0.001$) and the EMLA method ($p<0.05$). The mean VAS score during intralesional infiltration for the control method (T2) were 53.4±4.3, 17.8±2.9, and 33.9±3.9 for control group, skin cooling-method group and EMLA-method group, respectively. The mean VAS score during intralesional infiltration T2) for the skin cooling method was statistically significantly lower than the control method ($p<0.001$) and EMLA

Table 2. Demographic data of the study group

Parameter	Number
Number of patients	44
Age (year); mean (range)	39.98 (18 to 76)
BMI (kg/m^2); mean (range)	24.37 (17.51 to 42.63)
Sex (male:female)	3 (6.8%):41 (93.2%)
Location	
Ear	10
Neck	1
Back	2
Chest	10
Abdomen	5
Upper extremities	11
Lower extremities	4
Size	
Small (<5 sq.cm)	17
Medium (5 to 10 sq.cm)	21
Large (>10 sq.cm)	6

BMI=body mass index

Table 3. The visual analogue scale (VAS) of pain score at time when immediately needle piecing into the skin (T1)

Group	Mean	p-value
Control	4.2636	-
Skin cooling	1.0909	<0.001
EMLA	2.3386	<0.05

EMLA=Eutectic Mixture of Local Anesthesia

Table 4. The visual analogue scale (VAS) of pain score during infiltration of the corticosteroid (T2)

Group	Mean	p-value
Control	5.3386	-
skin cooling	1.7841	<0.001
EMLA	3.3955	<0.05

EMLA=Eutectic Mixture of Local Anesthesia

Table 5. The visual analogue scale (VAS) of pain score at 1 hour after infiltration of the corticosteroid (T3)

Group	Mean	p-value
Control	2.6023	-
Skin cooling	1.8409	>0.05
EMLA	2.2955	>0.05

EMLA=Eutectic Mixture of Local Anesthesia

Table 6. Satisfaction level of each pre-treatment

Group	Mean	p-value
Control	3.0682	-
Skin cooling	4.4091	<0.001 compare with control and EMLA
EMLA	3.3636	>0.05 compare with control

EMLA=Eutectic Mixture of Local Anesthesia

Table 7. The percentage of the preference pre-treatment methods for their future treatment

Pre-treatment method	n (%)
Skin cooling	37 (84)
EMLA	4 (9)
No treatment (Control group)	3 (7)
Total	44 (100)

EMLA=Eutectic Mixture of Local Anesthesia

method ($p<0.05$) (Table 4). There was no statistical significance of the mean VAS score at an hour after intralesional steroid injection (T3) (Table 5). The satisfaction level was statistically significant higher in skin cooling method compared to the control method ($p<0.001$) and EMLA method ($p<0.001$), but no statistical significance was found between the control method and the EMLA method (Table 6). Finally, 37 from 44 patients preferred the skin cooling method for their future pretreatment method (Table 7).

Discussion

Keloid is a fibroproliferative disorder of wound repair reflecting excess healing distinguished from hypertrophic scars by overgrowth of the scar tissue beyond the original wound edge. Keloid fibroblasts have an abnormal collagen synthesis, deposition, and accumulation. The underlying mechanisms of excessive repair are not yet known. Profibrotic cytokines such as transforming growth factor-β1 (TGF-β1)[2] and imbalances between fibroblast proliferation and apoptosis have been reported to be the causes of keloid formation[3]. Keloid scar is benign and not contagious, but sometimes accompanied by severe itchiness, pain, and changes in texture[4] leading to physical and psychological discomfort and severe negative effect on the quality of life[5].

Several clinical approaches have been proven to be effective for treating keloids such as excision and primary closure, steroid injection, radiation, cryotherapy, laser, antitumor, and immunosuppressive agent. However, current practice guidelines emphasize

the importance of multimodal therapy. Though few randomized studies existed, there is broad consensus on intralesional steroid injection as the first-line therapy in keloid treatment. The response rate of intralesional steroid injection when used as monotherapy is variable, with 50% to 100% regression and a recurrence rate of 9% to 50%[6-11]. Additionally, intralesional steroid injection can be used in combination with other treatments to get better results and less side effects. Steroid has been shown to inhibit fibroblast growth and proliferation, decrease TGF-β1 and insulin-like growth factor-1 (IL-1), and increase basic fibroblast growth factor (bFGF). TA is the common medication of steroid for keloid therapy. Initially, TA 10 mg/mL concentration is administered. If there was no response, then a 40 mg/mL concentration is substituted.

There are some disadvantages of corticosteroid injection including skin atrophy, telangiectasia, dyspigmentation, and pain during injection, which is the worst disadvantage. Because of abnormalities in small nerve fiber function[12] and dense unyielding tissue in keloid scars, the injection can cause intolerable pain and treatment discontinuity. Muneuchi et al found that nearly one-third of the patients abandoned treatment because of pain[13]. Therefore, many techniques of injection were proposed to reduce pain during injection.

The high speed of injection also caused pain during injection. The extremely low speed at 3 to 6 mL/hour, injection was recommended[14]. An injection of a mixture of anesthetic and TA has been advocated by many authors[15,16]. However, this has two demerits. Firstly, the injection procedure is over before the effect of anesthesia resulting in failure to reduce pain. Secondly, the increased volume of injection caused more pressure, therefore, is more painful[17]. The technique of field block with local anesthesia was recommended but the potential risk for new keloid formation is of concern[17,18]. The pretreatment with 60% Lidocaine tape was introduced by Tosa to reduce the pain[19]. Although, it was simple, it is impractical as it take 120 minutes before the onset of action.

EMLA and skin cooling have been widely used as topical anesthetic to minimized pain in many minor skin procedures. EMLA cream such as lidocaine 2.5% and prilocaine 2.5%, is an emulsion in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. Application of EMLA to intact skin under occlusive dressing, provides dermal analgesia by the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and by the accumulation of lidocaine and prilocaine in the vicinity of dermal pain receptors and nerve endings. Numerous studies have shown the efficacy of EMLA to reduce pain sensation[20,21]. However, EMLA must be left on the skin for at least 60 minutes to be effective, and this interval may not be practical or optimal[22].

Ice has been used for many years as a local anesthetic, and it is well known that ice can ease pain[23-25]. Ice is inexpensive, easy to use, fast, and readily available. There is very little waiting for ice to anesthetize the skin. Cold prevents the perception of the pain through its effect on sensory nociceptors and decreases the conduction time and synaptic activity in peripheral nerves[26].

Kuwahara et al compared the anesthetic effect of EMLA cream and ice in healthy volunteers' arm skin[27] and found that both EMLA cream and ice decreased the discomfort associated with needle injection. In that study, patients perceived that EMLA cream-controlled pain better than ice. EMLA cream was perceived as a more efficacious anesthetic in 35% of subjects, 5% perceived ice as more efficacious than EMLA cream, and 60% of the subjects perceived no difference in pain.

As far of the authors' knowledge, this was the first study designed to evaluate the efficacy of skin cooling for reducing pain during intralesional corticosteroid injection for keloid. Since keloid will be softer and require less forceful injection after the first injection, the patients may report less pain scores even using the same technique. The authors used cross-over design in randomized orders of three pretreatment modalities to eliminate confounding factor from sequencing. The present study used the same surgeon for every procedure to eliminate confounding factor from inter physician variability. Moreover, the comparison of pain scores between each method was analyzed individually to remove subjective bias from different pain threshold among subjects.

From the present study, the authors found that both EMLA and ice clearly decreased discomfort compared to the control, and skin cooling with ice was shown to decrease pain more efficaciously than EMLA. Skin cooling for three minutes can reduce pain at the time of needle insertion and during injection. Nevertheless, both skin cooling and EMLA have no effect on discomfort symptoms after injection. EMLA cream application is a useful pretreatment method, but it takes at least 60 minutes to be effective, this may not be practical and need more cost. Although, side effects of EMLA cream are usually mild and transient, they

include itching, burning, pain, pallor or blanching, erythema, edema, and purpura[28]. Contact dermatitis and contact urticaria have been reported[29,30].

Pretreatment with skin cooling is a very simple, inexpensive, readily available, and effective method. Besides, no significant effect on the quality of treatment and no adverse effect were detected. Most patients (84.1%) choose skin cooling for pretreatment in case of further steroid injections are needed. The reasons for choosing ice packing were more pain reduction and less waiting time compared to others. The reasons for choosing EMLA (4.1%) were more pain reduction and no cold-related pain. There was one case of a very large keloid affecting half of the anterior chest wall area. It was impractical for using ice packing as the patient would suffer from intolerable cold sensation.

Conclusion

Skin cooling method is simple and a cost-effective procedure to reduce pain at the time of needle piecing the keloid and during infiltration of TA. Regarding to the present research, skin cooling is recommended for pretreatment before intralesional steroid injection for keloid treatment. However, skin cooling of very large keloid is not possible and pretreatment with EMLA is an alternative.

What is already known on this topic?

To reduce the pain during injection, many pretreatment protocols are applied such as mixing corticosteroid with lidocaine, lidocaine tape, and EMLA.

What this study adds?

Skin cooling has been used to decrease skin sensation in various procedures such as physical therapy and laser treatment. This study demonstrated the efficacy of skin cooling in pain reduction during intralesional corticosteroid injection for keloid and hypertrophic scar treatment.

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Conflicts of interest

The authors declare no conflicts of interest.

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