TREATMENT OF KELOIDS AND HYPERTROPHIC SCARS BY COMBINED CRYOTHERAPY AND INTRALESIONAL TRIAMCINOLONE

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SUMMARY

Objectives: To evaluate the outcomes of combining cryotherapy and intralesional triamcinolone in the treatment of keloids and hypertrophic scars.

Methods: 60 patients (31 males and 29 females) with 266 keloids and 34 hypertrophic scars were enrolled and divided equally into 2 groups. Group 1 were treated with cryotherapy in combination with intralesional triamcinolone 20 mg/ml (treated group) and group 2 (control group) were treated with intralesional triamcinolone alone 20mg/ml. The duration of treatment for both groups was 12 weeks with 4 sessions. The assessment of therapeutic responses was made at baseline, after 4, 8, 12 and 16 weeks.

Results: After treatment, in terms of thickness, the keloids and hypertrophic scars responded significantly better to combined cryotherapy and triamcinolone than triamcinolone alone ($p < 0.05$): 1.3% had excellent improvement, 46.4% had good improvement and 41.2% had moderate improvement and 11.1% had little improvement. Meanwhile, in control group, the percentage for each degree of improvement were 1.4%, 16.7%, 55.6% and 26.4%, respectively. Ultrasound revealed an average reduction of scar height in treated group (2.4 ± 1.3 mm), which was higher than the result in control group (1.8 ± 0.4 mm) ($p < 0.05$). Side effects in treated group including pain, blister, hypopigmentation, longer healing time, acne, and troublesome with menstrual cycles were sometimes were reported. No significant side effects were reported in both groups.

Conclusion: Combining cryotherapy with injection of intralesional steroids appeared to be superior in comparision with intralesional steroids alone in treatment of keloids and hypertrophic scars without severe side effects.

Keywords: *Keloids, hypertrophic scars, cryotherapy, intralesional steroids.*

1. INTRODUCTION

Keloids are the result of an overgrowth of fibrous tissue (mostly collagen) that extend beyond the borders of the original wound. They may occur spontaneously, not regress, and usually recur after excision. Hypertrophic scars are similar, but are confined to the wound borders, never appear spontaneously and usually regress over time. As keloids and hypertrophic scars often go along with pruritus, contractures, pain, and movement limitation, even in some cases, keloids can become ulcerated and cancerous, the need for treatment is apparent and not solely based on cosmetic[1]. Keloids are benign hyperproliferations of dermal connective tissue. Injury of the deep dermis commonly results in scar formation. The physiologic wound healing

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progress consists 3 phase: inflammation, cell proliferation, and matrix remodeling[2].

Nowadays, various methods have been used, from non-invasive methods such as applying silicone gel combined with pressure to invasive methods such as intralesional injection with Corticosteroids, 5-FU, Verapamil, Interferons, Bleomycin, Botox A...; cryotherapy; lasers; surgery; radiotherapy; etc for treatment of the conditions. However, these therapeutic options need to prove more efficiency and reliability. Intralesional corticosteroid injections and cryotherapy, as well as a combination of these two methods are the most common therapeutic options[3]. In term of mechanism, cryotherapy causes destruction of microcirculation and apoptosis of fibroblasts in scars[4]. This procedure results in a localized dermal edema, which facilitates injections into the scar tissue as larger volumes can be applied more easily, thus enhancing the therapeutic effect[5]. Triamcinolone acetonide affects the scars by inhibition of the collagen biosynthesis and the proliferation of fibroblasts [1]. Overall, few studies have been conducted to evaluate the efficacy of the combination of the two treatments in the world but there are no studies in Vietnam up to now. For these reasons, we aimed to compare the therapeutic response of cryotherapy in combination with intralesional triamcinolone and intralesional triamcinolone alone in treating keloids and hypertrophic scars in Vietnam.

2. METHODS

2.1. Patients

60 patients with keloids and hypertrophic scars aged from 16 to 69 years old and treated in National Hospital of Dermatology and Venereology from July 2021 to August 2022. Total lesions were 266 keloids and 34 hypertrophic scars.

2.2. Methods

- Inclusion and exclusion criteria:

Patients aged 16 to 69 years old were enrolled in this controlled study. Exclusion criteria were listed below:

+ Scars with ulcers, eczema, bleeding, pustules.

+ Patients with systemic disease, contraindication to corticosteroids (hypersensitivity to triamcinolone acetonide or lidocaine, Cushing syndrome or pseudo-Cushing syndrome, active bleeding or peptic ulcer disease, active bacterial infections such as tuberculosis or disseminated fungal infections, chronic diseases such as uncontrolled diabetes, hypertension, severe heart failure, congenital or acquired immunodeficiency, etc).

+ Patients with contraindications to cryotherapy (cold urticaria, Raynaud syndrome, Cryoglobulinemia, etc.).

+ Patients did not comply or quit the treatment.

+ Patients in pregnancy or breastfeeding.

- Enrolled patients were equally assigned into 2 groups with different treatment.

- Treatment:

+ Treated group: The center of the lesion was sprayed continuously from a distance of 1 cm from the skin until the area was frozen. There was 2 - 3 freeze-thaw cycle using liquid nitrogen spray. The freeze time was 5 - 10 s each cycle. Then, 20 mg/ml triamcinolone acetonide intralesionally was injected in the lesions after cryotherapy. They were treated in 0, 4, 8, 12 weeks and follow-up to 16 weeks.

+ Control group: Corticosteroid injections with triamcinolone 20 mg/ml strength were given. The volume differed among the patients due to the various size of the keloids.

+ Corticosteroid treatment: Kenacort Retard 80mg/2ml from Bristol-Myers Squibb, manufactured in New York, USA.

+ Liquid nitrogen spray: Brymill Cry-Ac® Hand Held Liquid Nitrogen Cryospray 500ml.

- Sample size: Using the calculation applied for controlled clinical trial. The estimated proportion of patients in the treated group with potential therapeutic response is 84%, while the percentage for the control group is 50%. After calculation, our study recruited 30 patients for each group.

- Measurement:

+ Thickness: Measurement of the scar height at the thickest of the lesion by ultrasound in 0, 8 and 16 weeks.

+ The Vancouver Scar Scale score (VSS score) has been used extensively in literature since then to determine the various factors such as scar height or thickness, vascularity, pigmentation and pliability of the scar in 0 and 16 weeks.

+ The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. It is a 10 cm line with anchor statements on the left (no pain) and on the right (extreme pain)

- 0: No pain
- 1 - 3: Mild
- 4 - 6: Moderate
- 7 - 8: Severe
- 9 - 10: Extreme

- Outcome assessment:

+ Evaluate the reduction of the thickness of the scars:

- Excellent improvement (> 90%).
- Good improvement (75 - 90%).
- Moderate improvement (50 - 75%).
- Little improvement (< 50%).

+ Evaluate the change of the VSS score.

+ Pain during the procedure.

+ Side effects

3. RESULTS

3.1. Demographic and baseline characteristics

Table 1. Demographic and baseline characteristics

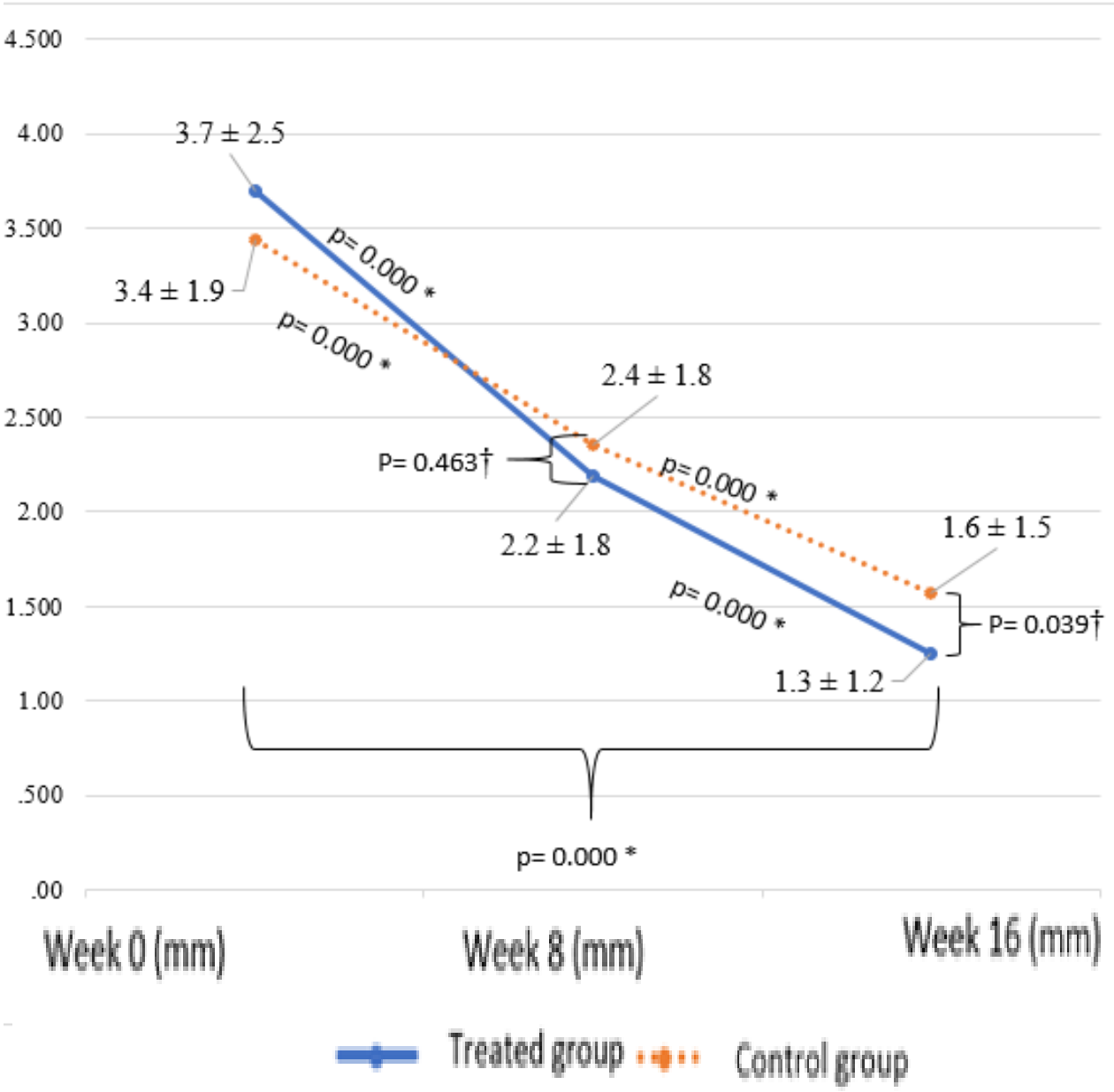
		Treated group (n = 30 patients)	Control group (n = 30 patients)	p
Sex	Male	18 (60%)	13 (43.3%)	0.196†
	Female	12 (40%)	17 (56.7%)	
Age (years)		25.6 ± 6.9	28.4 ± 11.5	0.257*
Average number of scars each person		4.9 ± 4.3	5.1 ± 3.1	0.837*
Type of scars	Keloids	133 (86.9%)	133 (90.5%)	0.332†
	Hypertrophic scars	20 (13.1%)	14 (9.5%)	
VSS score		5.8 ± 2.1	5.8 ± 2.2	0.766*
Thickness		3.7 ± 2.5	3.4 ± 1.9	0.343*

** The Independent Samples T Test, † The Chi-Square Test*

In our study, there were 31 male and 29 female participants. The mean of age in the treated group was 25.6 years old and 28.4 years old in the control group. The average number of scars each person was approximately 5 for both groups. At baseline, regarding sex, age, average number of scars each person, number of keloids, number of hypertrophic scars, VSS score and thickness had no significant difference between the two groups (p > 0.05).

3.2. Treatment outcome

3.2.1. Reduction of thickness scars

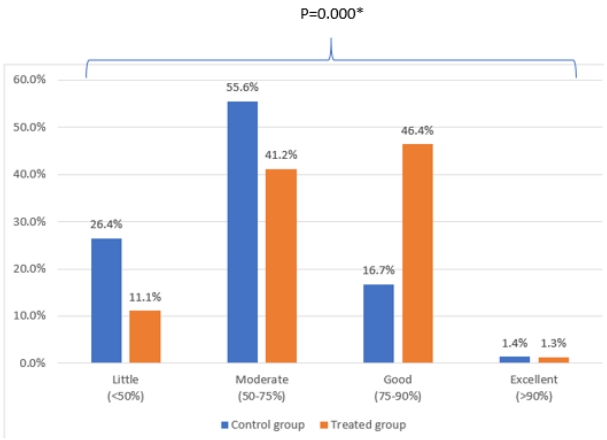


† The Independent Samples T Test; * The paired samples T Test

Figure 1. Reduction of thickness scars

The improvement of scar thickness in treated group were better than in control group, significantly, with $p < 0.05$ at week 16.

3.2.2. Changes in thickness scars

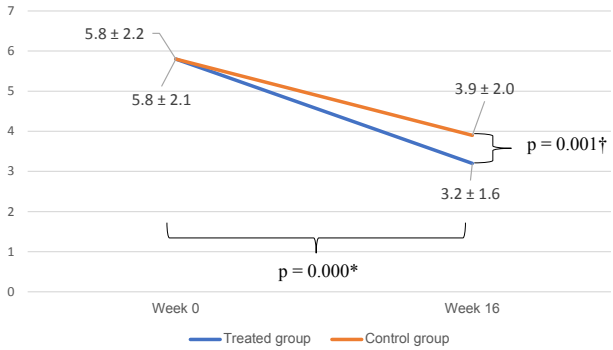


** Fisher's Exact Test*

Figure 2. Changes in thickness scars

The keloids and hypertrophic scars responded significantly better to combined cryotherapy and triamcinolone with triamcinolone alone (p < 0.05): 1.3% had excellent improvement, 46.4% had good improvement and 41.2% had moderate improvement and 11.1% had little improvement, meanwhile in control group the rates were 1.4%, 16.7%, 55.6%, and 26.4%, for each degree of improvement, respectively.

3.3.3. Changes in VSS



*† The Independent Samples T Test; * The paired samples T Test*

Figure 3. Changes in VSS

There was a significant decrease in the VSS of the scars in both groups 16 weeks after treatment compared to baseline (p < 0.05). At the end of treatment, the VSS of treated group was lower significant than control group (p < 0.05).

3.3.4. Pain and itch before and after treatment

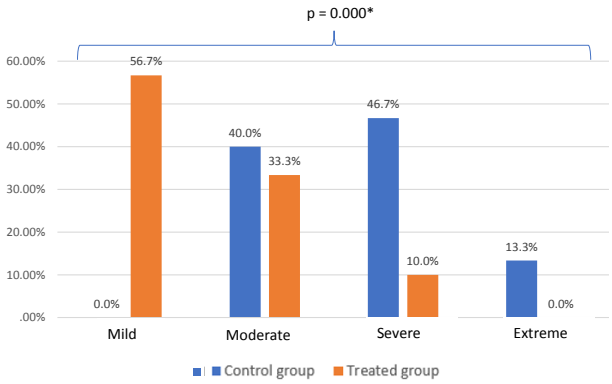
Criteria		Treated group (n = 153 scars)		Control group (n = 147 scars)		p
		n (%)	p	n (%)	p	
Pain	Week 0	31 (20.3)	0.000*	28 (19.0)	0.000*	
	Week 16	9 (5.9)		10 (6.8)		0.744†
Itch	Week 0	109 (71.2)	0.000*	104(70.7)	0.000*	
	Week 16	12 (7.8)		12 (8.2)		0.919†

*† The Independent Samples T Test; * The paired samples T Test*

Figure 4. Pain and itch before and after treatment

The number of painful and itchy scars were significantly lower after treatment compared to baseline in both groups. However, at week 16, no differences were noted between combined therapy and triamcinolone alone.

3.3.5. VAS score during the procedure



** Fisher's Exact Test*

Figure 5. VAS score during the procedure

The VAS score during the procedure in treated group were higher than in the control group. In treated group, there were 46.7% severe pain and 0.0% mild pain. Besides, there were 56.7% mild pain and 10.0% severe pain during the procedure in control group.

3.3.6. Side effects

Table 2. Side effects

	Treated group (n = 30 patient)	Control group (n = 30 patient)	p
Blister	105 (68.6%)	0 (0%)	0.000*
Hypopigmentation	39 (25.5%)	0 (0%)	0.000*
Hyperpigmentation	9 (5.9%)	17 (11.6%)	0.080*
Longer healing time	8 (5.2%)	2 (1.4%)	0.000*
Atrophy	0 (0.0%)	5 (3.4%)	0.027†
Telangectasia	11 (7.2%)	44 (29.9%)	0,000*
Acne	3 (10.0%)	4 (13.3%)	0.694*
Troublesome with menstrual cycles	3 (10.0%)	5 (16.7%)	0.456*
Changes of workup: CBC, biochemistry	2 (6.7%) (Hyperlipidemia)	3 (10.0%) (Hyperlipidemia)	0.647*

* The Chi-Square Test, †: Fisher's Exact Test

The most common side effects in the treated group were blistering (68.6% of the scars) and hypopigmentation (25.5%). Otherwise, in the control group, telangectasia and hyperpigmentation were the most common side effects, and the percentage of the scars were 29.9% and 11.6%, respectively. There were significant increases in blistering, hypopigmentation and longer healing time from the treated patients in comparision with the patients in control group.

4. DISCUSSION

The combination of cryotherapy and triamcinolone was found to be an effective treatment for flattening keloids. Our results showed that this combination was superior to triamcinolone injections alone. All patients from treated group, the mean thickness of the lesions is 2.2 ± 1.8 mm, 1.3 ± 1.2 mm at week 8 and week 16. In control group, the mean thickness is 2.4 ± 1.8 mm, 1.6 ± 1.5 mm at week 8 and week 16. This result was similar to the study of Hannah et al, after 16 weeks, the thickness was improved from 3.2 ± 1.2 mm at baseline to 2.2 ± 1.2 mm after treatment[6]. G Yosipovitch et al showed that after 3-8 treatment sessions, the reduction in thickness of the scar in treated group (7.7 ± 4.2 mm) was significantly better than control group (3.1 ± 2.2 mm) ($p < 0.05$)[7]. A possible explanation for the differences in treatment outcome in our study may be related to the number of treatment sessions.

The percentage in the treated group at week 16 were 1.3%, 46.4%, 41.2% and 11.1% at excellent, good, moderate and little degree, respectively. Our results are similar to the results from Saurabh et al[8]. As in Figure 3, the decrease of total VSS in the treated group is significantly better than the control group. This is the result of improvement of pigmentation, pliability, vascularity and height of the scars.

Keloidal tissue has induced the deposition of alpha globulin (collagenase inhibitors), which results in increasing collagen and glycosa aminoglycans synthesis. Corticosteroids show efficacy by reducing alpha globulins within the keloidal tissues and inhibit fibroblast growth[9]. The combination of cryotherapy and corticosteroids may promote the process by their microcirbulatory damaging effect and tissue necrosis. Adding cryotherapy prior to triamcinolone injection has been previously reported to bebeneficial since it causes edema, which allows the triamcinolone to be injected more effectively and less pain[10].

In our study, both methods had shown comparable efficacy in decrease of pain and itching of scars. In a study by Conway et al, corticoid reduced the painful and itchy scars, especially itchy scars[11]. In another study in 2016, G. Yosipovitch et al showed that triamcinolone acetonide alone or in combination with cryotherapy improved pain and itching of scars[7].

The cause of the itching and pain at the scar is thought to be due to the increased density of fibroblasts and collagen causing compression at the nerve endings in the scar tissue. In addition, there is a large number of mast cells at the scar, which release several mediators such as histamine that causes itching. Corticosteroids inhibit the activity of fibroblasts and reduce collagen synthesis, thus reducing nerve endings compression. Moreover, corticosteroids also have anti-inflammatory effects, reduce vascular permeability, stabilize mast cell membranes, so reduce the release of mediators, thereby reducing itching and pain at scars[12, 13].

There was a difference in pain intensity between our study and G. Yosipovitch at al[7]. This may be due to local anesthesia by Emla (lidocaine and prilocaine) 1 hour before procedure in their study[7]. Based on this finding, we recommend applying local or systemic anesthesia before cryotherapy with triamcinolone acetonide intralesional injection for more efficacy and less pain.

As in Table 2, the proportion of blister was 68.6% of total scars in treated group, while there was no case reported in the control group. In our patients, most of blister appeared 12 to 24 hours and yellow fluid after 1 to 3 days after procedure. The patients were instructed to puncture the blisters by a sterile needle without removal of the cover, rinse the lesion with NaCl 0.9%, apply antibiotic ointment and dress the wound. Our finding was similar to the result of Sonal et al with 63.64% of total scars in the patients treated by the combination[14]. In addition, the second common side effect was hypopigmentation. This is probably because the melanocytes are more susceptible to damage from freezing than keratinocytes, and their destruction can lead to depigmentation[15].

There were no serious side effects and no patient had to stop treatment because of side effects.

5. CONCLUSION

In conclusion, regardless of the mechanism, combination of cryotherapy and injection of intralesional steroids proved to be more efficacious than intralesional steroids alone in the treatment of keloids and hypertrophic scars without serious side effects.

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