

Efficacy of combination of intralesional corticosteroid injection and cryotherapy versus intralesional corticosteroid injection alone in patients of keloid

Md Qamrul Ahsan, Md Akram Ullah Sikder, Lubna Khondker

Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

Abstract

Objective To compare the efficacy of combination of intralesional corticosteroid injection and cryotherapy with intralesional corticosteroid injection alone in patients of keloid.

Methods A clinical trial was carried out in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh for duration of January 2013 to August 2013. About 30 patients (group A) were treated with intralesional triamcinolone acetonide with cryotherapy and 30 patients (group B) were treated with intralesional triamcinolone acetonide.

Results Improvement rate was highest for the lesions on the chest, which was 18 (34.6%) and lowest for back 3 (5.8%). Out of all patients from group A, the mean size of the lesions were 8.17cm, 5.90 cm, 4.32 cm, and 3.57 cm at 1st visit, 2nd visit, 3rd visit and 4th visit, respectively. In group B, the mean size of the lesions was 7.50 cm, 4.92 cm, 3.00 cm, and 4.75 cm at 1st visit, 2nd visit, 3rd visit and 4th visit, respectively. Among the patients of group A and B, 27 (90%) and 25 (83.3%) cases improved, respectively.

Conclusion Each of the treatment was individually effective in the treatment of keloid but study with a larger group of patients for longer period may result in superior outcome in clinical practice through improved compliance.

Key words

Efficacy of intralesional corticosteroid, cryotherapy, keloid.

Introduction

A keloid may be defined as a benign growth of dense fibrous tissue, usually developing from an abnormal healing response to a cutaneous injury, extending beyond the original borders of the wound or inflammatory response.¹ Clinically, they are firm nodules, which may be skin-colored, hypopigmented, or erythematous

secondary to telangiectasias.^{2,3} For unknown reasons, keloids occur more frequently among Blacks, Hispanics and Asians and less commonly in Caucasians.^{4,5} Keloids usually occur after trauma or wounding of skin.⁶ In addition to cosmetic disfigurement, keloids may cause protracted itch and pain resulting in a significant negative psychosocial burden for the patient.⁷ On histologic examination, keloids are found to have increased collagen and glycosaminoglycan deposition, both major components of the extracellular matrix.⁸

Clinicians always find it difficult to treat

Address for correspondence

Dr. Lubna Khondker, Associate Professor
Department of Dermatology & Venereology
Bangabandhu Sheikh Mujib Medical University
(BSMMU), Dhaka, Bangladesh.
Email: lubnaderma@gmail.com

keloids. Various therapeutic options have been used. Management of keloids has advanced from crude, invasive methods such as gross excision and radiation to intralesional or topical agents that act on a cellular level.⁹ Despite their common occurrence and the multitude of treatment modalities available, keloids remain a significant challenge for both the clinician and the patient.¹⁰ Despite the availability of many treatment modalities for the keloid, none has been found to be completely effective and satisfactory.¹¹ Steroids are known to inhibit collagen synthesis and fibroblast growth in vitro and possess anti-inflammatory properties.¹² Atrophy, one of the side effects of steroids, is utilized to achieve therapeutic effect in keloids.¹³ Intralesional steroid injection has a high degree of tolerability as well as effectiveness in reducing symptoms.¹⁴ It has been reported that treatment of fibroblasts with triamcinolone acetonide results in a reduction in TGF- β expression and an increase in FGF production.¹⁵

Cryotherapy is the application of extreme cold to treat or destroy keloids.¹³ Cryotherapy utilizes liquid nitrogen, upon evaporation, produces extreme cold, -196° . Application of liquid nitrogen to keloid tissue results in freeze destruction of keloid tissue.¹⁶ Cryotherapy has been used for smaller lesions, but its use is limited by considerable pain and sometimes prolonged healing following treatment.¹⁷ Cryotherapy has been reported to alter collagen synthesis and induce keloidal fibroblast differentiation towards a more normal phenotype.¹⁸ Some authors advocate the use of cryotherapy just prior to steroid injection in order to induce edema and thus facilitate steroid injection. Thus, in this controlled comparative study, the combined effect of intralesional corticosteroid injection with cryotherapy versus intralesional corticosteroid alone in the treatment of keloid was evaluated. Novel therapies deserve further investigation. This will likely lead to

more specific and effective treatment in the future.

Methods

A clinical trial conducted with sixty patients of keloid attended in the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka for duration of January 2013 to August 2013. Convenient type of non-probability sampling was followed. Patients were selected on the basis of inclusion and exclusion criteria. Inclusion criteria were age of the patients more than 12 years of age of either sex, having untreated keloids and patient who gave informed consent and willing to comply the study procedure. Exclusion criteria were patient with pregnancy, lactating mothers, who are under-treatment for keloids in past 12 weeks, suffering from keloid but those have contra-indications for cryotherapy, known case of corticosteroid sensitivity, patients with concomitant illnesses like renal failure, hepatic failure, peptic ulcer disease, diabetes and hypertension, and immunocompromised patients.

Procedure of the study The sample size of 60 patients was randomized into two groups. Group A, 30 patients were treated with intralesional triamcinolone acetonide with cryotherapy and in group B, 30 patients were treated with intralesional triamcinolone acetonide alone. Patients were divided into these groups by a randomization coding system derived from a computer-generated randomization table. Written informed consent was taken. Details of the patients, like name, age, sex, address, family history, presenting complaints, and history related to the keloid were recorded in the proforma. Baseline assessments were made by measuring the size using measuring tape. The patients received intralesional injections of triamcinolone acetonide with or without

cryotherapy for at least 3 sessions spaced 4 weeks apart. The intralesional corticosteroid injection protocol was as follows: triamcinolone acetonide 40 mg/ml was used. The corticosteroids were injected directly into the keloid with a 30 gauge needle attached to a 1 ml insulin syringe. The volume injected differed among the patients due to varying sizes of the keloids and ranged between 0.1 ml-0.5ml.

The cryotherapy treatment protocol was as follows: EMLA cream was applied to the keloid 1 hour before treatment. The center of the keloid was sprayed with liquid nitrogen from a distance of 1 cm from the skin until the field was frozen. Patients received cryotherapy at weekly intervals using hand-held cryosurgical unit, for a maximum of six sessions or 75% flattening which ever occur in earlier. Adjacent structures were covered using adhesive putty (clay) for protection. Patients were given two freeze-thaw cycles of 15 seconds freeze time each using spot freeze technique. In case of larger lesions, the field was divided into overlapping circles of 2 cm each. Each circle was then treated separately, treating not more than 16-8 cm² area at a time. Assessment was made one month after each treatment sessions. The parameters of the assessment included size of keloids (measured using measuring tape), and symptomatic improvement. No improvement when no flattening or <25% flattening and improvement when more than 25% flattening. Patients assessed the cosmetic appearance and the symptomatology for grading the improvement. During each visit, the size of the keloid was recorded in centimeters using the measuring tape. The clinical appearance was classified into the atrophic, hypertrophic or nodular categories. Other features like skin atrophy, erythema, ulceration, skin necrosis, hypopigmentation or hyperpigmentation, and other features were also recorded.

The strength of triamcinolone acetonide used for this study was 40 mg/ml, with up to a maximum of 2 ml per dose. The injections were scheduled at 4 weekly intervals for consecutive 3 months. Subsequently, the patients were instructed to follow up at monthly intervals for 3 months. The keloids were cleaned thoroughly with a spirit swab and the needle of the insulin syringe was inserted into the substance of keloid and the solution was pushed with adequate pressure till minimal blanching were seen. These were repeated at multiple sites on the keloid. At the end of the study, an attempt were made to analyze the effect of cryotherapy and triamcinolone acetonide in keloids and the various factors affecting the treatment outcome. Data were analyzed by computer with the help of SPSS software package. Statistical significance was set at 0.05 level and confidence interval at 95% level. Level of significance were measured by using appropriate procedures like chi square test (χ^2), relative risk (RR) measurement, students t-test, ANOVA tests and others where applicable. A *p* value less than 0.05 were considered to be significant.

Results

In group A, 30 patients were treated with intralesional triamcinolone acetonide with cryotherapy and in group B, 30 patients were treated with intralesional triamcinolone acetonide alone.

Table 1 showed age distribution of two groups, ≤ 15 years and >15 years. The two groups were well matched in term of age distribution.

Maximum patients of both groups gave negative personal history of trauma to skin before history of keloid. Only 13.3% and 10% patients of group A and group B, respectively gave the positive personal history of trauma. No statistical significant difference was observed

Table 1 Distribution of age among study groups.

Age in groups	Study groups				Total	
	Group A		Group B		n	%
	n	%	n	%		
≤ 15 Years	08	26.7	07	23.3	15	25.0
> 15 Years	22	73.3	23	76.7	45	75.0
Total	30	100.0	30	100.0	60	100.0

X² value = 0.089. df = 1. P = 0.766. Not Significant (> 0.05)

Table 2 Distribution of study groups by personal history of trauma to skin (n=60).

History		Study groups				Total		Significance.
		Group A		Group B		n	%	
		n	%	n	%			
Personal history of trauma to skin before	Present	04	13.3	03	10.0	07	11.7	X ² = 0.162 P = 0.688 NS
	Absent	26	86.7	27	90.0	53	88.3	
	Total	30	100.0	30	100.0	60	100.0	

Table 3 Distribution of study groups by duration of illness (n=60).

Duration of illness (months)	Group	n	Mean	± SD	Median	Range	Sign.
		Group A	30	10.00	7.24	08	2 – 36
	Group B	30	8.20	6.54	06	1 – 24	P = 0.316
	Total	60	9.10	6.90	06	1 – 36	NS

Table 4 Distribution of study groups by number of lesion (n=60).

Number of lesion	Study groups				Total	
	Group A		Group B		n	%
	n	%	n	%		
Single	15	50.0	14	46.7	29	48.3
Multiple	15	50.0	16	53.3	31	51.7
Total	30	100.0	30	100.0	60	100.0

X² value = 0.067. df = 1. P = 0.796. Not Significant (> 0.05)

Table 5 Distribution of recovery pattern among site of lesion (n=60).

Site of lesion	Recovery pattern				Total	
	Improved		Not improved		n	%
	n	%	n	%		
Chest	18	34.6	00	0.0	18	30.0
Ear	17	32.7	05	62.5	22	36.7
Extremities	10	19.2	00	0.0	10	16.6
Abdomen	04	7.7	03	37.5	07	11.7
Back	03	5.8	00	0.0	03	5.0
Total	52	100.0	08	100.0	60	100.0

X² value = 8.670. df = 4. P = 0.070. Not Significant (> 0.05)

Table 6 Distribution of clinical responses among the study groups(n=60)

Size of lesion (cm)	Study groups	mean	± sd	median	range	Significance
Before Treatment	Group A	8.17	3.11	08	3 – 15	t = 0.779
	Group B	7.50	3.51	07	1 – 20	P = 0.439
After Treatment / 2 nd visit at 4 th week	Group A	5.90	3.78	06	0 – 14	t = 0.104
	Group B	4.92	4.55	05	0 – 18	P = 0.918
After Treatment / 3 rd visit at 8 th week	Group A	4.32	4.34	05	0 – 12	t = 0.104
	Group B	3.00	5.52	00	0 – 18	P = 0.918
After Treatment/ 4 th visit at 12 th week	Group A	3.57	5.03	00	0 – 12	t = 0.104
	Group B	4.75	7.45	8.50	0 – 18	P = 0.918

Table 7 Distribution of recovery rate among the study groups(n=60)

Recovery Rate	Study groups				Total	
	Group A		Group B		n	%
	n	%	n	%		
Improved	27	90.0	25	83.3	52	86.7
Not improved	03	10.0	05	16.7	08	13.3
Total	30	100.0	30	100.0	60	100.0

X² value = 0.577. df = 1. P = 0.448. Not Significant (> 0.05)

Table 8 Distribution of duration of illness according to recovery pattern(n=60)

Duration of Illness (Months)		N	mean	± sd	median	range	Sign.
		Improved	52	7.38	4.47	06	1 – 24
Not improved	08	20.25	9.59	24	6 – 36	P = 0.007	
Total	60	9.10	6.90	06	1 – 36	HS	

between two groups (*p* value = 0.688).

Table 3 shows that out of all patients of group A, the duration of illness ranged from 2 months to 36 months, with an average of 10 months. In group B, the duration of illness ranging from 1 month to 24 months, with an average of 8.20 months. No significant difference is observed. (*p* value = 0.316). **Table 4** shows the distribution of number of lesions of both groups of patients. Single lesion was 15 (50%) for group A and 14 (46.7%) for group B. Multiple lesions were 15 (50%) and 16 (53.6%) for group A and group B, respectively. No significant difference is observed (*p* value = 0.796).

Table 5 shows the recovery pattern according to the site of distribution of lesions. Improvement rate was highest for the lesions on the chest, in 18 (34.6%) patients and lowest for back in 3 (5.8%) patients. Improvement rate for ear was 17 (32.7%), for extremities 10 (19.2%) and abdomen 4 (7.7%). No improvement was found for the lesions on the ear and abdomen, which was 5 (62.5%) and 3 (37.5%), respectively. No statistical significant difference is observed between two groups, *P* value = 0.070 (> 0.05)

Table 6 showed the clinical responses among the study groups. Out of all patients from group A, the mean size of the lesions was 8.17cm, 5.90 cm, 4.32 cm, and 3.57 cm at 1st visit, 2nd visit,

3rd visit and 4th visit, respectively. In group B, the mean size of the lesions was 7.50 cm, 4.92 cm, 3.00 cm, and 4.75 cm at 1st visit, 2nd visit, 3rd visit and 4th visit, respectively. No statistical significant difference is observed between two groups.

Table 7 shows the recovery rate after treatment. Among the patients of group A and B, 27 (90%) and 25 (83.3%) patients improved, respectively. The number of failure was 3 (10%) and 5 (16.7%) for group A and group B, respectively. No statistical significant difference was observed between the two groups, *P* value = 0.448 (>0.05).

Table 8 depicts the statistical analysis of all improved patients in both groups and duration of keloid ranging from 1 month to 24 months (mean 7.38 months). The not-improved patients had duration ranging from 6 months to 36 months (mean 20.25 months). Statistical significant difference was observed between improved and not-improved patients, *P* value = 0.007 (< 0.05).

Discussion

Our study observed that in group A, 8 (26.7%) patients aged ≤15 years and 22 (73.3%) >15 years. For group B, 7 (23.3%) patients were ≤15 years and 23 (76.7%) were >15 years, similar to

the study of Yosipovitch *et al.*¹⁹ and El-Tonsy *et al.*²⁰ Yosipovitch *et al.*¹⁹ conducted a study with adolescents aged between 15 to 18 years with at least 2 keloids of at least 1 year duration were entered into the study after providing informed parental consent.¹⁹ El-Tonsy *et al.*²⁰ observed that the age of the patients ranged between 2-65 years. In our study, out of all patients of group A, the duration of illness was ranged from 2 months to 36 months. In group B, the duration of illness ranged from 1 month to 24 months. Our results differed from the study of Barara *et al.*¹ and Yosipovitch *et al.*¹⁹ Barara *et al.*¹ conducted a study with 30 patients of keloids with duration of keloids under study ranged from 1-15 years. Yosipovitch *et al.*¹⁹ conducted a study with the mean duration of the keloids were 3.5 (range 1-4) years.

Improvement rate was highest for the lesions on the chest, 18 (34.6%) and lowest for back 3 (5.8%). No improvement was found in the lesions on the ear and abdomen, 5 (62.5%) and 3 (37.5%) cases, respectively. Barara *et al.*¹ observed that anatomical site of keloids and etiology did not have any significant correlation with treatment outcome, either at 3 or at 6 months.

Out of all patients from group A, the mean size of the lesions reduced i.e. 8.17cm, 5.90 cm, 4.32 cm, and 3.57 cm at 1st visit, 2nd visit, 3rd visit and 4th visit, respectively. In group B, the mean size of the lesions was 7.50cm, 4.92cm, 3.00 cm, and 4.75 cm at 1st visit, 2nd visit, 3rd visit and 4th visit, respectively. Barara *et al.*¹ showed that after 6 treatment sessions, the average flattening increased to 58.13% and average thickness reduced further to 0.213cm. The flattening of keloids varied from 12-100%. Softening was observed in all lesions except an earlobe keloid.¹ Yosipovitch *et al.*¹⁹ showed that in terms of thickness, the keloids responded significantly better ($p < 0.001$) to combination therapy

compared with intralesional triamcinolone alone or cryotherapy alone. Layton *et al.*² conducted a study with acne keloidalis, in which intralesional triamcinolone or cryosurgery was used as treatment for keloids. They demonstrated that by treating early, and in particular vascular keloids, 85% were showed a moderate to good response in terms of flattening. Treatment with intralesional triamcinolone was also beneficial, but the response to cryosurgery was significantly better in early, vascular lesions. Prabhu *et al.*⁴ conducted a study with 29 patients. In the 15 patients who were treated with triamcinolone acetonide, the mean reduction in volume was 71.23%.

Among the patients of group A and B, 27 (90%) and 25 (83.3%) improved, respectively. El-Tonsy *et al.*²⁰ observed that 8 (44%) patients showed good response with satisfactory cosmetic result. Five (28%) patients showed poor response with poor cosmetic result and many complications. In the combined cryosurgery and intralesional corticosteroids injection group, 8 (32%) patients showed excellent results. Ten (40%) patients showed good result and 7 (28%) patients showed poor response with poor cosmetic result. On the other hand in cryosurgery group, amongst idiopathic lesions, 33.3% showed good results, and 66.7% poor results. Secondary lesions showed 42.3% excellent results, 42.3% good results, and 15.4% poor results.²⁰

Our study showed that all improved patients from both groups had the duration of their keloids ranging from 1 month to 24 months (mean 7.38 months). The not-improved patients had the duration ranging from 6 months to 36 months (mean 20.25 months), similar to the study of Barara *et al.*¹ They observed that duration and thickness of keloid correlated positively with treatment outcome (P value: 0.000 and 0.023, respectively). For analyzing the

effect of duration on treatment outcome, keloids were divided into 3 groups: group A: duration less than 3 years; group B: duration ranging from 3-6 years; group C: duration more than 6 years. A better percentage flattening of 51% was noted in group A lesions after 3 treatment sessions as compared to 24.5% flattening in group B and 15.8% in group C keloids. At 6 months, the percentage flattening was still highest in group A. Recent onset keloids had an early response with maximum flattening obtained in first 3 months. In contrast, older keloids with duration more than 3 years showed an initial slow response with maximum flattening being observed in the latter half of therapy.¹ El-Tonsy *et al.*²⁰ showed that the duration of the lesion represented an important parameter in the response of the lesion to both treatment modalities. In cryosurgery group, younger lesions (<1 year) responded well to cryosurgery followed by intralesional corticosteroid injection, as 66.7% of them showed excellent results, 33.3% showed good response, with no poor results. Older lesions (1-5 years) showed no excellent results, 50% showed good results and 50% showed poor response. Old lesions (>5 years) showed 16.6% excellent results, 41.7% good results and 41.7% poor response.²⁰

Conclusion

In the light of the findings of the study we conclude that each of the treatment is individually effective but study with a larger group of patients for longer period may result in superior outcome in clinical practice through improved compliance. Further multicenter, randomized, double-blind study should be conducted with large sample size.

References

1. Barara M, Mendiratta V, Chander R. Cryotherapy in treatment of keloids:

- Evaluation of factors affecting treatment outcome. *J Cutan Aesthet Surg.* 2012;**5**:185-9.
2. Layton AM, Yip J, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. *Br J Dermatol.* 1994;**130**:498-501.
3. Sharma S, Bhanot A, Kaur A, Dewan SP. Role of liquid nitrogen alone compared with combination of liquid nitrogen and intralesional triamcinolone acetonide in the treatment of small keloids. *J Cosmet Dermatol.* 2007;**6**:258-61.
4. Prabhu A, Sreekar H, Powar R, Uppin VM. A randomized controlled trial comparing the efficacy of intralesional 5-fluorouracil versus triamcinolone acetonide in the treatment of keloids. *J Sci Soc.* 2012;**39**:19-25.
5. Mutalik S. Treatment of keloids and hypertrophic scars. *Indian J Dermatol Venereol Leprol.* 2005;**71**:3-8.
6. Shepherd JP, Dawber RP. The response of keloid scars to cryosurgery. *Plast Reconstr Surg.* 1982;**70**:677-81.
7. Zouboulis CC. Principles of cutaneous cryosurgery: An update. *Dermatology.* 1999;**198**:111-7.
8. Ruscioni L, Rossi G, Bono R. Use of cryotherapy in the treatment of keloids. *J Dermatol Surg Oncol.* 1993;**19**:529-34.
9. Cruz NI, Korchin L. Inhibition of human keloid fibroblast growth by isotretinoin and triamcinolone acetonide in vitro. *Ann Plast Surg.* 1994;**33**:401-5.
10. Robles DT, Moore E, Draznin M, Berg D. Keloids: Pathophysiology and management. *Dermatol Online J.* 2007;**13** (3):9.
11. Pollack SV. Treatment of keloids. In: Wheeland RG, Ed. *Cutaneous Surgery.* Philadelphia: WB Saunders; 1994. p. 688-98.
12. Manuskiatti W, Fitzpatrick RE. Treatment response of keloids and hypertrophic sternotomy scars. *Arch Dermatol.* 2002;**138**:1149-55.
13. Berman B, Flores F. Recurrence rates of excised keloids treated with post operative triamcnenolone acetonide injections or interferon α 2b injections. *J Am Acad Dermatol.* 1997;**37**:755-7.
14. Malakar S, Malakar R. Intralesional cryosurgery: Consequences, cautions and precautions. *Indian J Dermatol.* 2000;**45**:100-1.

15. English RS, Shenefelt PD. Keloids and hypertrophic scars. *Dermatol Surg*. 1999;**25**:631-8.
16. Kill J. Keloids treated with topical injection of triamcinolone acetonide (Kenalog), Immediate and long-term results. *Scand J Plast Reconstr Surg*. 1977;**11**:169-72.
17. Bock O, Schmid-Ott G, Malewski P, Mrowietz U. Quality of life of patients with keloid and hypertrophic scarring. *Arch Dermatol Res*. 2006;**297**:433-8.
18. Kelly AP: Medical and surgical therapies for keloids. *Dermatol Ther*. 2004;**17**:212-8.
19. Yosipovitch G. A Comparative Study of Combination Intralesional Corticosteroid with Cryotherapy versus Intralesional Corticosteroid and Cryotherapy Alone in the Treatment of Keloids in Adolescents. *J Dermatol Surg Oncol*. 1999;**5**:54-6.
20. El-Tonsy MH, Anber TE, El-Domyati MM, El-Din WH. Evaluation of ND-YAG Laser Versus Combined Cryotherapy and Intralesional Corticosteroid Injection in Treatment of Keloids and Hypertrophic Scars. *Semin Cutan Med Surg*. 1999;**18**:159-71.