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Original Article

Comparison of Therapeutic Response of Keloid to Intralesional Injection of Triamcinolone Acetonide and Bleomycin

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Abstract

Background: Keloids are an aberration of normal healing process. Majority of the cases are symptomatic and indolent to treat. Though there is no ideal monotherapy, intralesional injection of triamcinolone acetonide is one of the first line treatment. Triamcinolone has a variable sensitivity, chance of complication and recurrence. As an emerging novel treatment, intralesional application of bleomycin shown promise in several studies. **Materials and Methods:** Single blind comparative study done at Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh from February, 2019 to August, 2020. Purposive sampling of 50 adult patients with keloid were enrolled, later by lottery with sealed envelope were done, to allocate into two groups A and B. They were given intralesional injection of triamcinolone acetonide and bleomycin every four weeks respectively. Both groups were assessed before and followed up every two months for a total of six months after completion of three dose of intralesional infiltration. Outcomes were compared against each other as per Vancouver scar scale score, numeric rating scale score for pain and itching. **Results**: Majority of the subjects (23) belonged to 18-24 years age group. In group A (triamcinolone acetonide), mean Vancouver scar scale score remission rate was 34.46% and In group B (bleomycin), it was 49.6% over 6 months follow up. Remission rate of pain in group B was 92%, while in group A it was 42%. Remission rate of itching in group B was 77.7% and in group A it was 34.2%. **Conclusion:** Intralesional injection of bleomycin is better for the treatment of keloid than triamcinolone acetonide.

Keywords: Keloid, Intralesional, Bleomycin, Triamcinolone acetonide.

Introduction

Keloid is a benign fibro-proliferative disorder which results from an up-regulation of collagen synthesis, deposition and accumulation. It is a cicatricle lesion that extends beyond the limits of the trauma, with invasion of adjacent healthy tissue. There is significant impairment of quality of life for patients, with physical, motor, aesthetic and psychosocial sequel. There are multiple treatment methods for keloids. Despite several reported strategies, no standard treatment protocol exists.Intralesional injection of corticosteroid triamcinolone acetonide (TAC) is one of the first line treatment modalities for keloid treatment.[1] It could promote vasoconstriction in the keloid scar and control local inflammation by reducing expression of TGF ß receptors.[2] Though triamcinolone acetonide (TAC) has been the first line agent for treatment, its response rates vary with higher recurrence rates.[3,4] Despite good tolerance, a significant fraction of keloids are steroid resistant. Recent studies shown hope in treatment of steroid resistant as well as steroid sensitive cases with intralesional injection of bleomycin.

Materials and Methods

A single blind comparative study carried out at Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh from February, 2019 to August, 2020. Due to time constraints and unavailability of the patients

due to COVID19 pandemic total 50 samples with keloid were selected aged between 18-50 years were enrolled by purposive sampling, later by lottery with sealed envelope were done to allocate into two groups A and B. They were given total 3 doses of intra-lesional injection of triamcinolone acetonide and bleomycin every four weeks apart respectively. Both groups were assessed before and followed up every two months for a total of six months after completion of three dose of intralesional infiltration. Outcomes were compared against each other as per Vancouver scar scale score (VCSSS),[5] (Annexure-01) Numeric rating scale score (NRSS) for pain[6] and itching[7]. Post infiltration complications were also compared. Both group A and B included 25 subjects. Prior to the infiltration, detailed history regarding natural history of the keloid, co-morbidities and possible contraindications were recorded, photograph taken and VCSSS for keloid scar evaluation, NRSS for pain and itching were recorded in semi structured questionnaire form. All infiltration procedures were done by the investigator with standard asepsis under protection of personal protection gear at operative complex. Insulin syringe 100 IU was used for infiltration. Both groups were infiltrated with local anesthetic (2% lidocane) at lesion site before injecting with study drugs.

In group A, Triamcinolone acetonide was diluted with 0.9% saline solution and given at 20mg/ml concentration into the papillary dermis until skin blanching is produced. Maximum dosage in a single setting was not more than 120mg to avoid systemic side effects.

Patients of Group B were given intradermal injection of bleomycin by the investigator in a dose of 0.5-1 ml/cm^2 with maximum dose of 6mg (6IU) per session at 1.5mg/ml concentration. Each 15mg (15IU) lyophilized powder of bleomycin sulfate vial dilution was carried out by mixing the powder with 10 cc 0.9% saline solution. Infiltration of both group stopped after total 3 doses or when Vancouver scar scale become 0 or in case of any major complication.

Clinical assessment was carried out using Vancouver scar scale score that includes vascularity, pigmentation, pliability and height. Height was measured by using a slide calipers. The results were recorded from 0 to 14 where 0 reflected normal skin. Pain and itching were assessed as per NRSS. Complications following infiltration were also recorded.

Findings of observation and interview with the patient and attendants were recorded in preformed data collection sheet using a pre-designed structured questionnaire and were filled up by the investigator. Data from both groups were collected before first session of infiltration. Following intervention follow up was done by the investigator and data were recorded accordingly. Besides the local examination findings, the records also included pre-infiltration and post-infiltration photograph of the involved part.

In group A, TAC was given at a concentration of 20mg/ml. Maximum dosage of TAC in a single setting was not more than 30mg (1.5 ml). Dilution of bleomycin was carried out by mixing the 15 mg of powder with 10 cc 0.9% saline solution. It was given at a concentration of 1.5 IU/ml without exceeding the maximum dose of 6 IU. In this study, both groups were infiltrated with local anesthetics prior to infiltration. A total of 3 doses were given at 4weekly interval but infiltration of both groups were stopped when Vancouver scar scale become 0 or in case of any major complication.

Annexure-01: Outcome measurement by The Vancouver Scar Scale.

Sl. No	Criteria	Clinical findings	Score
1	Vascularity	Normal	0
		Pink	1
		Red	2
		Purple	3
2	Pigmentation	Normal	0
		Hypo-pigmentation	1
		Hyper-pigmentation	2
3	Pliability	Normal	0
		Supple	1
		Yielding	2
		Firm	3
		Ropes	4
		Contracture	5
4	Height	Flat	0
		<2mm	1
		2-5mm	2
		>5mm	3
	Total score		13

Results

Majority of the subjects 23(46%) belonged to 18-24 years age group. (Table –I)

Table I: Distribution of the respondents by age group (n=50)

Age Group (years)	Frequency (n)	Percentage (%)
18–24	23	46.0
25-34	17	34.0
35-44	7	14.0
45-50	3	6.0
Mean age	28±8	
Range	18-50	

Table II: Distribution of the respondents by family history (n=50)

Family History	Frequency (n)	Percentage (%)
Negative	44	88
Positive	6	12
Total	50	100.0

6(12%) cases had a positive family history. (Table-II)

Table -III: Distribution of the respondents by site of keloid (n=50)

Site	Frequency		Percentage (%)
	Group A	Group B	
Neck	2	1	6
Ear lobule	3	0	6
Shoulder	2	4	12
Pre-sternal area	2	4	12
Anterior trunk	2	3	10
Back	1	4	10
Upper limb	8	4	24
Lower limb	5	5	20
Total	25	25	100.0

Maximum 12(24%) of the respondents had keloid over upper limb followed by 10(20%) over lower limb and 6(12%) over shoulders. (Table-III)

Table IV: Distribution of the respondents by previous treatment modality (n=50)

Previous history of treatment	Frequency		Total Percentage (%)
	Group A n (%)	Group B n (%)	
Steroid	10(40)	8(32)	36
Surgery	2(8)	5(20)	14
Other	1(4)	3(12)	8
None	12(48)	9(36)	42
Total	25(100)	25(100%)	100

Majority of the respondents 42% had no treatment for keloid and 36% patient took intralesional triamcinone (Table-IV)

Table V: Distribution of the respondents by duration of keloid (n=50)

Duration of keloid (months)	Frequency		Percentage (%)
	Group A	Group B	
6	6	5	22
7	4	5	18
8	2	1	6
9	3	1	8
11	0	1	2
12	4	4	16
13	0	1	2
14	3	0	6
16	0	1	2
18	0	2	4
20	0	1	2
24	1	2	6
36	0	1	2
180	1	0	2
480	1	0	2
Total	25	25	100

Majority of the respondents had keloid for 6 months . (Table-V)

Table VI: Comparison of pre-intervention numeric rating scale score (NRSS) for pain mean and follow up scores between group A & group B (n=50)

Visits	Group A NRSS for pain mean ± SD	Group B NRSS for pain mean ± SD	Total NRSS for pain mean ± SD
Pre-intervention	4.16±2.76	3.92±2.8	4.04±2.75
1st Follow up	3.6±2.3	2.76±2.12	3.2±2.22
2nd Follow up	3±2.18	1.32±1.28	2.16±1.9
3rd Follow up	2.4±2.08	0.6±0.91	1.5±1.8

Table VII: Mean remission of NRSS for pain from pre-intervention state to 3rd follow up between group A & group B

Groups	Mean pre-intervention NRSS for pain	Mean 3rd F/U NR SS for pain	Mean remission	Remission rates (%)	P value
Group A	4.16	2.4	1.76	42.3	.000
Group B	3.92	0.6	3.32	92.3	

Remission rate of itching in group B from pre-intervention state to 3rd follow up was 92.3%, while in group A it was 42.3% (p=.000). Table-VII

Table VIII: Mean remission rate of NRSS for itching from pre-intervention state to 3rd follow up between group A & group B

Visits	Group A NRSS for itching mean ± SD	Group B NRSS for itching mean ± SD	Total NRSS for itching mean ± SD
Pre-intervention	4.68±2.2	5.04±2.4	4.86±2.3
1st Follow up	4.28±2.2	3.72±1.8	3.1±2.1
2nd Follow up	3.64±2.2	2.56±1.3	3.1±1.4
3rd Follow up	3.08±2.1	1.12±1.1	2.1±1.9

Table IX: Mean remission rate of NRSS for itching from pre-intervention state to 3rd followup between group A & group B

Groups	Mean pre-intervention NRSS for itching	Mean 3rd F/U NRSS for itching	Mean remission	Remission rates (%)	P value
Group A	4.68	3.08	1.6	34.18	.000
Group B	5.04	1.12	3.92	77.77	

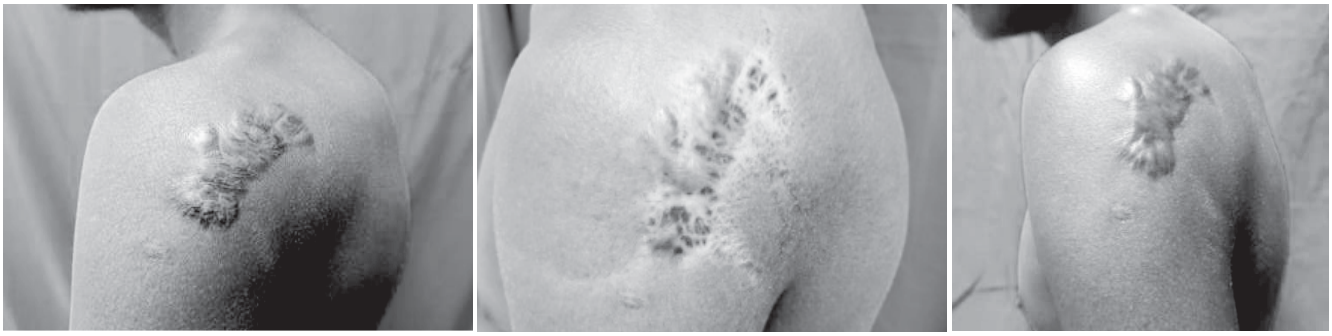
Table-VIII and IX In group A (triamcinolone acetonide), mean Vancouver scar scale score was found initially 9.4±2.29, after final follow up it became 6.16±2.6 with remission rate of 34.46%. In group B (bleomycin), initial mean score was 10.3±1.91, after final follow up it became 5.2±2 with a remission rate of 49.6% (p=.002).

Table X: Comparison of mean pre-intervention VCSSS and 3rd follow up VCSSS between group A & group B

Groups	Pre-intervention VCSSS mean ± SD	3rd Follow up VCSSS mean ± SD	Mean reduction rate of mean VCSSS at 3rd follow up	Remission rate(%) as per mean VCSSS at 3rd follow up	P value
A (n=25)	9.4±3.39	6.16±2.26	3.24	34.4%	.002
B (n=25)	10.32±1.91	5.2±1.94	5.12	49.6%	
Total (n=50)	9.86±2.1	5.76±2.2	4.12	41.78%	

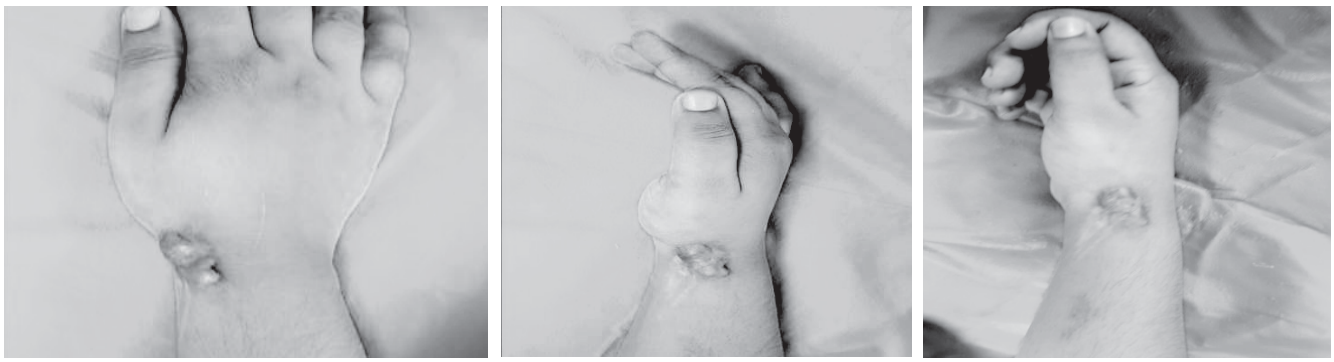
Remission rate of itching in group B from pre-intervention state to 3rd follow up was 49.6%, while in group A it was 34.4% (p=.000). (Table-X)

Figures



A. Pre-Intervention picture Group-B B. 1st follow up picture Group-B C. 3rd follow up picture Group-B

Fig 1: (A- C) Pre-intervention and follow up pictures of a group B respondent.



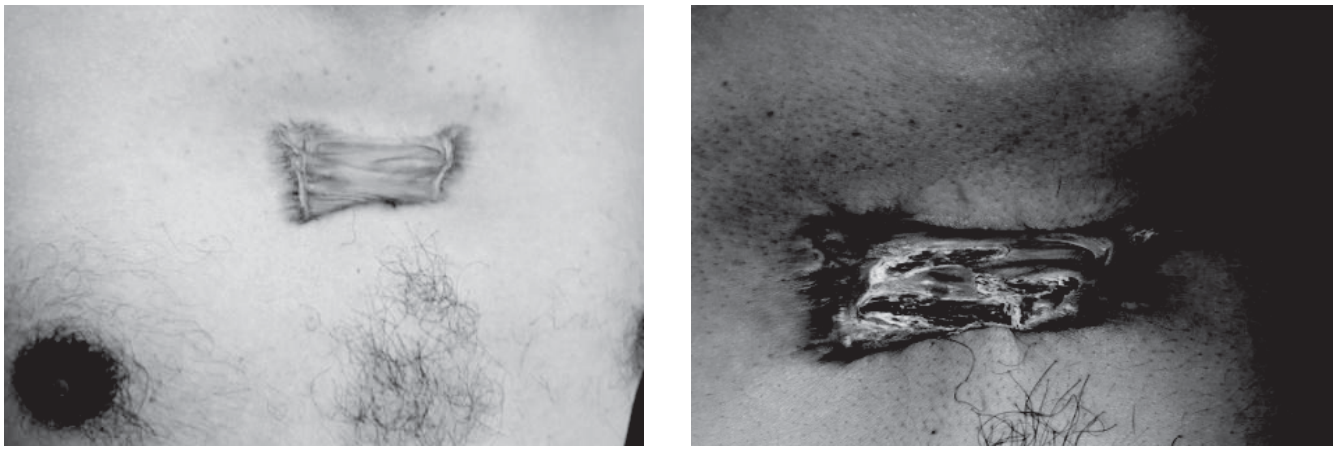
A. Pre-Intervention picture Group-A B. 1st Follow up picture Group-A C. 3rd Follow up showing remission Group-A

Fig 2 :(A-C) Pre-intervention and follow up pictures of a group A respondent.

Table XI: Distribution of Complications after infiltration (n=50)

Complication	Frequency (n=50)	
	Group A	Group B
Skin ulceration	0	3
Hypo-pigmentation	6	0
Hyper-pigmentation	0	5
Skin atrophy	2	1
Telangiectasia	2	0
Total(Percentage)	40%	36%

High rate of complications were observed in this study (Group A 40% & Group B 36%).(Table-XI)



A. Before infiltration of bleomycin B. One week after first infiltration of bleomycin

Fig 3 :(A-B) Pre-intervention and follow up pictures of a group B respondent showing skin ulceration

Discussion

In this study, the mean age of the study cases was 28±8 years. Minimum age of the patients was 18 and maximum age of the patients was 50 years. Among the study cases maximum 23 (46%) patients were in 15-24 years age group. In a similar study found (Dash et al. 2010)[8] The highest percentage of the patients was in the age group 20-24 years (27.6%). Group A had 10 (40%) male and 15(60%) female subjects. Group B had 10 (40%) female and 15(60%) male subjects. This is a reflection of scar awareness among male patient also.The most common etiology of keloid in this study was burn 22 (44%) followed by trauma 19 (38%) and infection 9(18%). In a similar study by Hietanen [9] three most common etiologies were surgery (46%), acne scars (25%), and traumatic wounds 9.8% . Majority of the subjects had keloid over upper limb 12(24%). Lower limbs 10(20%), Back 6(12%) & shoulder 5(10) are other common site for keloid.

According to Kabel et al[10], The most common affected sites were mainly chest, shoulder, back, forearm and neck.The mean duration of keloid in this study was 23.82±70.29. Group A had a mean of 35.24±98.18. Group B had a mean of 12.4±7.48. Maximum duration of keloid was 480 months and minimum duration was 6 months. In Reddy et al[11] the duration of keloid ranged from 3 to 14 (mean 6.6) years.There is no

previous keloid treatment history among 42% (21) subjects. Other 58% (29) had treatment. From group A, 10 (20%) took steroid injection, 2(4%) had surgery. From group B, 8 (16%) took steroid injection, 5(10%) had surgery. In a study by Dash et al[8] found 31% subjects took steroid, 36% surgery, 7% both and 26% took no previous treatment. The mean of pre intervention numeric rating scale for pain score was(n=50) 4.04±2.72, Maximum pain score was 8 and minimum were 0, Mean for group A was 4.16±2.76 , Mean for group B was 3.92±2.8.After final follow up, mean pain score was (n=50) 1.5±1.8. Maximum pain score was 7 and minimum were 0, Mean for group A (n=25) was 2.4±2.08, Mean for group B (n=25) was 0.6± 0.9. A study with bleomycin by Saray and Güleç[12] showed Complete resolution of pain in (67 %) cases.

On the other hand, The mean of pre intervention itching score was (n=50) 4.86±2.3, Maximum NRSS for itching was 8 and minimum were 0, Mean for group A was 4.68±2.2, Mean for group B was 5.04±2.4. After final follow up, Maximum itching score was 7 and minimum were 0, Mean for group A (n=25) was 3.08±2.1, Mean for group B (n=25) was 1.12±1.1.In a similar study found the complete resolution of itching in (80 %) cases.[12] In group A, VCSS score mean was found in pre-intervention 9.86±2.1, after final follow up it became 5.76±2.2 with remission rate of 41.78% . In group B mean score was 10.3±1.91, after final follow up it became 5.2±1.94 with a remission rate of 51.45%. Espana et al[13] found 54% complete flattening with a similar study with bleomycin. In group A, 6 cases (24%) of Hypopigmentation were found, and 2 cases (8%) of simultaneous Skin atrophy & telangiectasia (n=25). which is similar to a study.[14] In Group B, there were 5 cases (20%) of Hyperpigmentation, 3 cases (12%) of skin ulceration.

In similar studies, most common complication noted was minor ulceration which healed within 10 days and hyperpigmentation that resolved after 1 year of follow up.[12]

Conclusion

Following post-infiltration observation of the patients, it can be concluded that overall outcome, aesthetic outcome and rate of complications were different on both group. Bleomycin showed statistically better response in terms of Vancouver scar scale score, numeric rating scale score for pain & itching which proved to be effective intralesional agent than TAC but it has some reversible complication like skin ulceration and hyper-pigmentation where TAC had more hypopigmentation, irreversible skin atrophy and telangiectasia. So it is reasonable to say that bleomycin is a better alternative than TAC in treatment of keloid.

Limitation of the study

- The sample size was not large to infer the findings in general population.
- All data were collected from a single tertiary care center.
- Long term follow up was beyond scope of this study.

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