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The Efficacy of Bleomycin for Treating Keloid and Hypertrophic Scar

Bothaina Mahrous Ghanem, Laila Ahmed Sharaf, Mai Shams El-din Attwa*, Sara Hamdy Fouad
Department of Dermatology, Andrology and STDs, Faculty of Medicine, Mansoura University, Egypt
*Corresponding Author: Mai Shams El-din Attwa, **Mobile**: (+20) 01113326277, **Email**: rosem5078@gmail.com

ABSTRACT

Background: Keloids are benign fibroproliferative lesions characterized by abnormal collagen deposition within a skin injury. Keloid occurs as a result of an exaggerated tissue response to skin injury in a genetically-predisposed individual. Bleomycin is an anti-cancer agent that has been utilized for treating keloids and hypertrophic scars. It inhibits collagen synthesis and activates apoptosis of fibroblasts.

Objective: To assess the effectiveness and the safety of bleomycin for treating keloids and hypertrophic scar.

Patients and Methods: This was a prospective randomized experimental study, carried out on forty patients with keloid or hypertrophic scars. Dermatological examination included **c**omplete clinical assessment of lesions to determine the distribution, clinical variants and the extent of lesions. Assessment of keloid was done by Vancouver scar scale (VSS). The Patient and Observer Scar Assessment Scale (POSAS) were utilized to evaluate the efficacy of treatments. No recurrence was observed after six months follow up.

Results: Sixty% of the patients were females. The commonest cause for lesions was surgery, there was a significant improvement in POSAS and VSS after treatment, 52.5% of the patients showed improvement percentage >75% and other 40% showed improvement percentage 50-75%, 50% of the patients had excellent satisfaction while 42.5% had good satisfaction, the most frequently reported adverse effect was hyperpigmentation.

Conclusion: Bleomycin is a safe and effective method for treating keloids and hypertrophic scars.

Keywords: Keloid, Bleomycin, Hypertrophic Scar, Vancouver Scar Scale, Patient and Observer Scar Assessment Scale.

INTRODUCTION

Keloids are benign fibroproliferative lesions characterized by abnormal collagen deposition within a skin injury. Keloid occurs as a result of an exaggerated tissue response to skin injury in a genetically-predisposed individual [1].

These lesions are more common in dark-skinned people and are mainly found in those of African, Asian, and Hispanic descent [2]. Keloids can occur at all ages however it is more common in those aged 10 and 30 years. Keloids are commonly formed over the sternum, earlobes, shoulders, ankles, and/or face [3].

There are many available treatments for keloids including pressure therapy, topical applications, intra-lesional corticosteroid injection and surgical excision. These therapeutic options can be utilized either as monotherapy or in combination [4].

The treatment of keloid using traditional therapeutic options is challenging. Novel therapeutic options, such as bleomycin, are gaining great interest and extensive use [5]. Bleomycin is an anti-cancer agent that has been utilized for treating keloid and hypertrophic scars. It suppresses collagen synthesis, activates apoptosis of fibroblasts, and inhibits DNA synthesis [6,7], few studies have showed that keloids and hypertrophic scars are improved by intra-lesional injection of bleomycin [8,9].

This study aimed at evaluating the effectiveness and safety of bleomycin for treating keloids and hypertrophic scars.

PATIENTS AND METHODS

This was a prospective randomized experimental study that enrolled forty patients with keloid or

hypertrophic scars attending the Outpatient Clinic (OPC) of Dermatology, Andrology and STDs Department, Mansoura University Hospital.

We included patients with keloid or hypertrophic scars aged between 10 to 50 years. But we excluded pregnant or lactating females, patients with previously-treated keloid scars (in the previous six months), previous allergy from bleomycin injection and with hepatic, renal or peripheral vascular diseases. Y

Methods

Each patient was subjected to personal history (name, age and gender), complaint analysis, present history (Onset, Course, Percentage of body surface area involved, and Duration of the disease), past history **(**autoimmune skin diseases, malignancy, previous operations), medical history (Drug history, diabetes or hypertension**),** and family history of similar conditions.

A thorough general examination was done to detect predisposing factors, co-morbid conditions and to exclude chronic inflammation. Dermatological examination included **c**omplete clinical assessment of lesions to determine the distribution, clinical variants and the extend of lesions, assessment of keloid by VSS [10]**.**

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All patients with keloids and hypertrophic scars had been injected with intra-lesional bleomycin 1.5 IU/mL (diluted in 0.9% saline) with a maximum of 6 mL per session. The injections had been repeated monthly over six months. Photographs had been obtained before treatment in each session and at 24 weeks of follow-up.

Follow Up

Adverse effects of injection had been recorded during, immediately post-injection and subsequently at the time of follow up. The POSAS had been utilized to evaluate the effect of bleomycin injection on keloid.

The POSAS comprises 2 numerical scales that assess symptoms and signs of healing. It is composed of 2 scales: a scale for the patient and another one for the observer. Both components contain 6 items punctuated from 1 to 10, which comprise the "overall score" of the scale for both patients and observers. Each item assesses a particular parameter. Furthermore, patients and observers also mark their "general opinion" irrespective of the "overall score", also scored from 1 to 10. Each item on the two scales has a score of 1 to 10. The lowest score is 1, which indicates normal skin. The overall score (ranging from 6 to 60) was calculated by adding the scores of each of the 6 items.

Ethical approval:

Mansoura Medical Ethics Committee of the Mansoura Faculty of Medicine gave its approval to this study. All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical Analysis

Data were analyzed by Statistical Package for the Social Sciences (SPSS) v18 for windows. Qualitative data were described as number and percent, while quantitative parametric data were described as means ± standard deviations. Quantitative data was first tested for normality using one-sample Kolmogorov-Smirnov test in each study group then inferential statistic tests were selected. $P<0.05$ was considered significant.

RESULTS

Table **(1)** shows that 60% of patients were females, the mean age was 37.15 ± 12.69 years and mean BMI (kg/m^2) was 26.83 ± 4.79 kg/m^2. The commonest cause was surgery (45%) followed by trauma (37.5%), 17.5% of the patients had a positive family history while 42.5% of the patients had underlying disease.

The most common site was extremities (52.5%) followed by abdomen (27.5%). Keloids and hypertrophic (HT) scars mean duration was 37.86 ± 51.6 months and 20% of the patients had previous treatment (steroids).

Table (1): Demographic data, causes distribution, clinical characteristics, site distribution, keloids and HT scars characteristics of the studied population

Variable		**The studied patients** (n=40)
Age Mean ± SD		37.15 ± 12.69 years
Sex	Males	16 (40%)
	Females	24 (60%)
BMI (kg/m2) Mean ± SD		26.83 ± 4.79
Causes Distribution		
Vaccine		2 (5%)
Trauma		15 (37.5%)
Surgery		18 (45%)
Others		5 (12.5%)
Family history		
Positive		7 (17.5%)
Negative		33 (82.5%)
Associated Systemic Disease		
Yes		17 (42.5%)
No		23 (57.5%)
Site distribution		
Abdomen		11 (27.5%)
Chest		6 (15%)
Neck		2 (5%)
Extremities		21 (52.5%)
Keloids and HT scars characteristics		
Disease duration (months) Mean ± SD		37.86 ± 51.6
Previous treatment		
Yes		8 (20%)
No		32 (80%)

Table **(2)** shows that the most common symptom was pain (42.5%) followed by disfigurement (25%).

Table (2): Symptoms distribution among the studied patients

	The studied patients (n=40)
Discomfort	8 (20%)
Disfigurement	10 (25%)
Burning sensation	9 (22.5%)
Itching	12 (30%)
Erythema	3 (7.5%)
Pain	17 (42.5%)

Table **(3)** shows that there was a significant improvement in POSAS and VSS after treatment.

Table (3): Clinical evaluation before and after treatment of the studied patients

	The studied patients (n=40)		P
	Before	After	
POSAS Mean ± SD	90.13 ± 11.25	38.67 ± 5.52	**<0.001**
VSS Mean ± SD	9.41 ± 1.53	2.65 ± 0.884	**<0.001**

Table **(4)** shows a significant positive correlation between POSAS with VSS and duration. No association was found between POSAS with age, sex, and site. There was no significant correlation between VSS and other data.

Table (4): Correlation between POSAS and VSS after treatment and other data among the studied patients

	The studied patients (n=40)			
	POSAS		**VSS**	
	r	P	r	P
Age	0.167	0.211	0.201	0.185
BMI	0.188	0.2201	0.161	0.216
Duration	0**.288**	**0.043**	0.274	0.106
VSS	0**.537**	**0.001**		
Sex				
Male (n=16)	91.42 ± 12.31	0.861	9.18 ± 1.74	0.526
Female (n=24)	90.78 ± 10.46		9.52 ± 1.58	
Site				
Abdomen (n=11)	91.27 ± 11.38	0.839	9.27 ± 1.43	0.917
Chest (n=6)	90.52 ± 10.67		9.44 ± 1.79	
Neck (n=2)	89.56 ± 7.91		8.86 ± 1.75	
Extremities (n=21)	92.15 ± 12.44		9.24 ± 1.42	

r:Spearman correlation coefficient

Table **(5)** shows that 52.5% of the patients showed improvement percentage >75% and 50% of the patients had excellent satisfaction.

Table (5): Improvement percentage distribution and Patient satisfaction among the studied patients

	The studied patients (n=40)
Improvement percentage	
> 75%	21 (52.5%)
50 – 75%	16 (40%)
10 - 50%	3 (7.5%)
< 10%	0
Patient satisfaction	
Excellent	20 (50%)
Good	17 (42.5%)
Moderate or minimal	3 (7.5%)
Poor	0 (0%)

Table **(6)** shows that the most common side effect was hyperpigmentation (70%) while pain was 55%. On follow up of patients for 6 months, no recurrence was observed. Longer period of follow up may be recommended to exactly assess the recurrence.

Table (6): Side effects distribution among the studied patients

	The studied patients (n=40)
Hyperpigmentation	28 (70%)
Pain	22 (55%)
Pruritus	15 (37.5%)
Recurrence	0 (0%)

DISCUSSION

Wound healing is a dynamic process of balanced regulation. When such regulation is unbalanced, undesirable scar lesions such as hypertrophic scars and keloids can occur. These lesions are raised and firm scars that are formed as a result of increased synthesis of fibrinogen and collagen during healing [11]. Hypertrophic scar and keloid can be symptomatic, mainly, pruritic and can also be painful and cause movement restriction and cosmetic disfigurement. The hypertrophic scar is contained within the injury site and may regress over time, whereas the keloid can spread beyond injury borders and do not regress [12].

Hypertrophic scars and keloids arise from skin injuries that go deep enough to influence the dermis. They can form after burn, surgery, insect bite, tattooing, acne or chickenpox, and piercings [13]. There are several available treatments for keloid lesions and hypertrophic scars. Non-surgical options include intra-lesional steroid injection, bleomycin, 5-fluorouracil, and cryotherapy. Intra-lesional steroid injection can be utilized as first-line therapy [14].

The present study enrolled forty patients with keloid or hypertrophic scars attending to the clinic of Dermatology, Andrology and STDs Department, at Mansoura University Hospital, to evaluate the efficacy and safety of bleomycin in treating keloid and hypertrophic scar. In our study, 60% of the patients were females and 40% were males, which agreed with **Kassi *et al.*** [15] who reported that females were affected in 68.33% of cases vs. 31.67% were males with a sex-ratio of 0.46**.** Also, **Lu *et al.*** [16] reported male to female ratio 1:1.3.

However, it is usually supposed that males and females are equally likely to develop keloid scars with females are more likely to seek treatment because of social factors, namely, that females care more about the appearance, are less resistant to medical examination [17].

The mean age of the patients in our study was 37.15 ± 12.69 years, which agreed with **Kassi *et al.*** [15] who revealed that, the mean age was 34.20 years**.** Hypertrophic scars and keloids are exceptional among elderly and are very common in young people and

around puberty [18]. Though the correlation between skin color, pigment and keloids remains not completely understood, it has been demonstrated that dark-skinned individuals have a greater incidence of keloids. The prevalence of keloids among individuals of African, African American and Hispanic origin ranges from 5-16%, in Asian people it is 0.1–1% while in European and North American population it is less than 0.1% [19]. The higher prevalence in these groups is linked to a familial tendency to develop keloid scar and the presence of keloid scar in identical twins suggest the role of genetic factors [20].

In our study, 17.5% of patients had a positive family history while 42.5% of the patients had associated systemic disease. **Kassi *et al.*** [15] reported that 38.8% of their cases reported family and personal histories of keloid scars. The tendency to develop keloid lesions can be familial, studies have demonstrated that 5-10% of European people with keloids particularly severe lesions have a positive family history, at least one other family member has a keloid lesion [21].

The present study showed that mean disease duration was 37.86 ± 51.6 months. Also, **Lu *et al.*** [22] revealed that the mean duration of their investigation was 1.9 years. On the other hand, **Liu *et al.*** [19] found that the mean disease duration was 12.33±9.68 years. The present study showed that mean BMI was 26.83 ± 4.79 kg/m^2. which agreed with **Noishiki *et al.*** [23] who found that the mean BMI for male cases was 22.8 ±3.3 kg/m^2 and mean BMI for females was 21.3±3.3 kg/m^2.

The commonest cause of keloids and hypertrophic scar in the present study was surgery and trauma, which occurred in 45%, and 37.5% of cases respectively, which agreed with **Yoo and Kim** [24] who revealed that surgery and trauma were the commonest causes of scaring and keloid lesions. Less common causes in our study were vaccines in 5% of cases, while **Noishik *et al.*** [25] had revealed that the commonest triggers of keloid formation in males and females was vaccination, BCG vaccine was the most common type. Chickenpox was the second most common trigger in males (17.9%) and females (20.4%), followed by surgery (6.4%), trauma in (4.3%), which disagreed with our results.

In this study, the commonest site of keloids and hypertrophic scars was extremities in 52.5% followed by abdomen in 27.5%, chest was 15% and neck was 5%, which agreed with **Liu *et al.*** [26] who revealed that keloid and hypertrophic scars were detected mainly in the upper limbs (64.3% for keloid; 52.1% for hypertrophic scar), followed by face and cranium, then chest and abdomen.

Our study showed that 20% of the patients had previous intralesional steroids treatment. Also, **Yoo and Kim** [24] reported that 63% received previous treatment with intralesional steroid injection.

The current study revealed that the most common symptom was pain in 42.5% of cases followed by itching in 30%, disfigurement in 25%, burning sensation in 22%, discomfort in 20% and redness in 7.5%. **Kassi *et al.*** [15] found that keloids were accompanied by pruritus in 95%, pain in 53.33 % of cases, and suppuration/ulcers in 19.17%. Functional and psychological (with anxiety reported by patients) symptoms were reported by 33.33% and 65.83% of patients, respectively. In addition, **Huu *et al.*** [9] found hyperpigmentation in 56.7%, blisters in 78.3% and ulcers in 5.8%. While **Khan *et al.*** [27] reported hyperpigmentation in 70%, and ulceration in 27%.

In this study, there was a significant difference in the POSAS and VSS before and after treatment from 90.13 ± 11.25 to 38.67 ± 5.52 and from 9.41± 1.53 to 2.65 ± 0.824 respectively, denoting significant improvement in POSAS and VSS. Both scales were correlated, as the improvement in POSAS was associated with improvement in VSS. **Khan *et al.*** [27] had demonstrated a statistically significant difference between intra-lesional bleomycin, which had more efficacy compared with intra-lesional triamcinolone acetonide for treating keloid scars. Mean baseline POSAS score was improved in bleomycin group and even after 24 weeks follow up, still improved higher than triamcinolone acetonide group.

Kabel *et al.* [28] revealed a significant difference in the mean percentage change of VSS pre- and post-treatment between bleomycin-treated cases and 5-fluorouracil-treated cases, demonstrating that bleomycin had more efficacy than 5-fluorouracil. **Huu *et al.*** [9] reported that bleomycin improved the vascular condition by 70.6% following treatment (mean VSS decreased from 1.7 ± 1 to 0.5 ± 0.6) and mean VSS of stiffness decreased by 89.3% which agreed with our results.

On the other hand, **Wu *et al.*** [29] meta-analysis revealed that combination medications achieved more efficacy for treating scars compared with monotherapy, with botulinum toxin A and triamcinolone acetonide (TAC) and TAC+5-flouriuracil being most effective. In the majority of studies, BTA+TAC combination significantly improved the scar height and patient POSAS, VSS, and VAS than bleomycin injection alone.

In addition, **Rao *et al.*** [30] found that bleomycin was more effective than TAC combined with 5-flouriuracil for treating keloids or hypertrophic scars; however the difference was non-significant between the groups.

Our study revealed a significant positive association between POSAS with VSS and duration i.e. with increase duration of keloid there was increase in POSAS after treatment i.e., less response. Also, with less POSAS there was less VSS after treatment. But no association was found between POSAS with age, sex, and site with no significant correlation between VSS and other data.

Chae *et al.* [31] found that the association between the VSS and POSAS was significant. The observer scale demonstrated significant correlation with patient's ratings for the individual categories. In VSS, pliability, height, and overall score showed significant correlations with the patient's components of stiffness,

thickness, and total scores. Also, **Yoo and Kim** [24] did not find a significant correlation between patient's characteristics (e.g. family history and medical disease) and symptoms (pruritus and pain) with diagnosis of keloid lesions or hypertrophic scars.

The present study revealed that 52.5% of the patients showed improvement percentage >75% while 40% showed improvement percentage 50 – 75% and only 7.5% showed improvement percentage < 50%. The present study revealed that 50% of the patients showed excellent satisfaction while 42.5% showed good satisfaction and only 7.5% showed moderate or minimal satisfaction. **Kim *et al.*** [14] found that bleomycin showed more significant improvement of scars compared with TAC. Furthermore, there was significant improvement of cases in the bleomycin group compared with those treated with 5-flouriuracil or TAC combined with cryotherapy. They suggested that bleomycin was more effective than other treatments. **Payapvipapong *et al.*** [32] studied two groups; the first group included fractional CO_2 laser with topical bleomycin and the second group included fractional CO_2 laser with topical triamcinolone. They reported that clinical improvement did show statistical significance. As regards patient's satisfaction score, 50% of both groups reported an acceptable improvement. There was no statistical difference in terms of photographic and ultrasonographic assessment between both groups.

In the present study, the most common side effect was hyperpigmentation (70%) while pain was 55% and pruritus was 37.5%. **Moravej *et al.*** [33] reported that ulceration (53.8%), hyperpigmentation (76.9%), and secondary infection (34.6%) were the most common side effects respectively. **Bik *et al.*** [34] reported that the commonest adverse effects of local bleomycin injection were pain and hyperpigmentation. The pain is usually more severe with bleomycin injection due to its sclerosing effect. Local anaesthesia prior to injection is often required to relieve pain. Novel methods such as the micropuncture, microneedling pen, laser-assisted drug delivery, and needle-free pneumatic injection have been used to alleviate the pain. The redness, edema, and burning of the injection site are often temporary.

The present study found no recurrence was observed after 6 months of follow up. Longer periods of follow up may be recommended to exactly assess the recurrence. **Kabel *et al.*** [28] reported that patients treated with bleomycin had a significantly lower recurrence compared to those treated with 5-flouriuracil. Furthermore, **Rao *et al.*** [30] had found that patients treated with bleomycin had a significantly lower recurrence compared to those treated with TAC + 5-flouriuracil, however the difference was insignificant. In contrast, **Huu *et al.*** [9] reported that the rate of recurrent scars after bleomycin injection treatment were high (14%), and that main sites of recurrence were in the chest wall, the front aspect was statistically higher compared to other surgical areas. No relationship existed between pre-treatment thickness and recurrence risk.

In general, intra-lesional bleomycin achieved acceptable results for common warts, keloid scar, hypertrophic scar, propranolol-resistant haemangiomas, and corns [34]**.** However, in most trials focused on bleomycin treatment for common warts, intra-lesional bleomycin achieved higher cure rates compared to cryotherapy [35].

The current study had some limitations, including a limited sample size and the fact that bleomycin treatment was not compared to other effective treatments for hypertrophic scars and keloid. Subject heterogeneity, including gender, familial history, keloid and HTS location, skin tension, size, and quantity, as well as Fitzpatrick skin type, may all have a role in keloid response. Case-control and split scar studies are both effectively controlled, and randomization with at least evaluator blinding will increase evidence quality. The Dermatology Life Quality Index can also be used to assess patient satisfaction and quality of life. More multicenter research on trials of bleomycin injection alone should be done, as well as long-term efficacy evaluations.

CONCLUSION

Bleomycin is a safe and effective method for treating keloids and hypertrophic scars.

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