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ORIGINAL ARTICLE

Intralesional Injection of Bleomycin in The Treatment of Keloids.

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ABSTRACT

Background: Keloid is a common clinical distressing problem. Its treatment is a challenging process due to its high rate of recurrence and resistance to some therapies. The aim of this study is to evaluate the efficacy and safety of intralesional injection of bleomycin in the treatment of keloids.

Methods: Ten patients with keloid lesions were included in this study. Patients were injected every 2 weeks for 6 sessions using intralesional injection of bleomycin at a concentration of 1.5 IU/ml in normal saline solution with a maximum dose of 6 ml per session.

Results: The results were satisfying as percentage of improvement after treatment was 60% according to Vancouver score and was (80% & 87.5%) according to pain and pruritus scores respectively.

Conclusions: Intralesional injection of bleomycin is an effective and safe modality in the treatment of keloids.

Key words: Keloid; Intralesional; Bleomycin.

INTRODUCTION

Vitiligo is the most common depigmentation disorder with an overall estimated worldwide prevalence of 0.5 to 2%, characterized by white macules on the skin caused as a result of the systematic destruction of functional melanocytes.

The pathophysiology of vitiligo is thought to start by a trigger event that instigate stress responses in the skin , eliciting an autoimmune response in genetically susceptible individuals that ultimately targets the melanocytes known to have an inherited fragility, predisposing individuals to develop vitiligo. **[2,3]**

Oxidative stress supposed to be one of the triggering events in melanocyte degeneration in vitiligo. Melanogenesis produces significant levels of reactive oxygen species (ROS). ROS along with other radicals can induce oxidative stress. **[4]**

Malondialdehyde (MDA) arising from the free radical degradation of polyunsaturated fatty acids, can cause cross-linking in lipids, proteins and nucleic acids. Lipid peroxidation in melanocyte cell membrane may play an important role in depigmentation of vitiligo. **[5]**

AIM OF THE WORK

The aim of study is to evaluate serum levels of MDA in vitligo patients compared to healthy controls.

SUBJECTS AND METHODS

Patients: Twenty five patients with vitiligo were included in this case control study. Along with twenty five age and sex matched healthy subjects were taken as controls. The study was conducted in Dermatology outpatient clinics and Biochemistry department, Faculty of Medicine, Zagazig University Hospitals, spanning period from April 2018 to October 2018.

Written informed consents obtained from the patients participating in the study. The study had approval of the Institutional Review Board (IRB) in Faculty of Medicine, Zagazig University (ZU-IRB#4531/6-4-2018).

Patients with vitiligo of any type or extent , any age ,both sexes are included in the study. Exclusion criteria included Pregnant and lactating females.

Methods: All participants were subjected to complete history taking, general and dermatological examination to detect type and sites of vitiligo. Vitiligo European Task Force assessment (VETFa) was calculated to assess the three dimensions of the disease (extent (area), staging and spreading). Area is divided into head and neck (0-9%), trunk (0-36%), lower limbs (0-36%), upper limbs (0-18%) , hand and feet are included in evaluation of extent in upper and lower limbs. Staging is divided into stage 0: normal pigmentation, stage 1: incomplete depigmentation, stage 2: complete depigmentation, may include hair whitening in a minority of hairs <30%, stage3: complete depigmentation with significant hair whitening >30% and Stage 4: complete hair whitening. Spreading is divided into +1

progressive, 0 stationary and -1 regressive. Total area is the summation of all areas, total staging is the summation of staging of all areas and total spreading is the summation of spreading of all areas. **[6]**

Specimen collection and storage:

Three ml of venous blood were taken from each participant in the morning without fasting under complete aseptic condition then put in a sterile, dry, clean separator gel tube for serum isolation and left to clot. After clotting, the samples were centrifuged for 10 minutes at 5000 rpm. Serum was separated and stored at -20˚C in blood bank to detect MDA.

Measurement of Malondialdehyde spectrophotometerically.

Malondialdehyde in serum sample was calculated by the following equation.

MDA in Serum sample = $\frac{\text{sample}}{\text{standard}} \times 10$ nmol. **[7]**

Statistical analysis:

Data analysis was performed using the software SPSS version 20. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies. Chi square test and Fisher test were used to compare the proportion of categorical data. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. Non-parametric test (Mann Whitney) was used to compare means in two groups. To compare means of more than two groups, Kruskal wallis test was used. To find the correlation between two continuous variables which are normally distributed, Spearman correlation coefficients was used according to type of data. The level statistical significance was set at $P<0.05$. Highly significant difference was present if $p \leq 0.001$.

RESULTS

Twenty five patient with vitiligo was included in the study,their age ranged from 13-56 years with a mean ± SD of 39.88 ± 16.15, male to female ratio 1.5: 1, along twenty five age and sex healthy controls, their age ranged from 16-55 years with a mean ± SD of 33.16 ± 11.68, male to female ratio 1.5: 1. There was no statistical significant differences between the two studied groups in age or sex distribution.

Regarding clinical data of patients group, 44% showed generalized vitiligo, 24% focal, 16% acrofacial, 12% segmental and 4% mucosal. Family history was +ve in 44% of cases. 96% of cases showed progressive course. Duration of disease ranged from 0.17-22 months with a mean ± SD of 7.23 ± 7.26. Patients have previous ttt in the form of phototherapy (56%), topical corticosteroid (48%) and calcineurin inhibitors (20%). Regarding VETFa, 36% was stage 4, 32% stage 2, 24% stage 10, 4% stage 3 and 4% stage 1. 40% was spread 2, 32% spread 1, 24% spread 5 and 4% spread 0. Percentage area involved ranged from 2-76% with a mean ± SD of 20.82 ± 22.92. As shown in **table (1) , figure (1).**

Serum malondialdehyde level in vitiligo patients ranged from 3.4-18.9 with a mean ± SD of 10.7 ± 4.4. MDA level of control group ranged from 2.1-7.7 with a mean ± SD of 4.56 ± 1.11. There was highly statistical significant difference between studied groups regarding MDA level ($p \leq 0.001$). As shown in **table (2) , figure (2).**

There was a negative correlation between disease duration and malondialdehyde ($p>0.05$). As shown in **table (3).**

There was a negative correlation between malondialdehyde with spreading and staging scores, while there was a positive correlation between malondialdehyde and percentage area ($p>0.05$). As shown in **table (4)**.

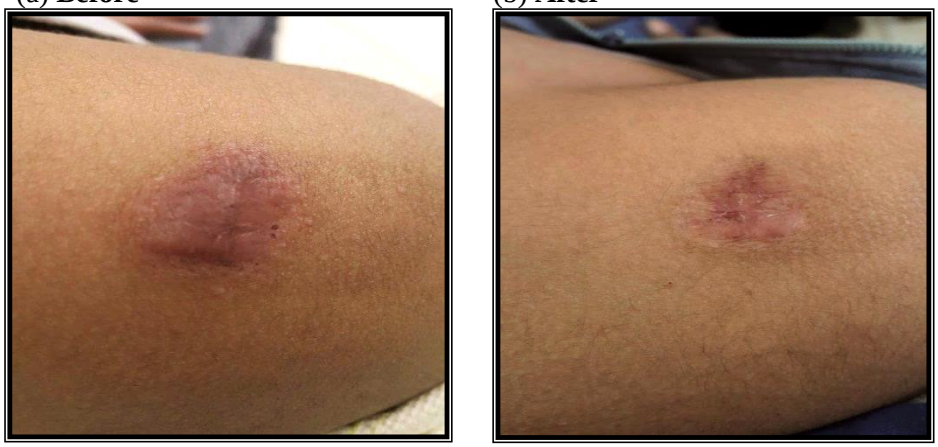
Table (1): Comparison of Vancouver Scale, Pain and Pruritus scores in patients before and after treatment.

Keloids scores		**Bleomycin (n=10)**	**p**
Vancouver Scale score	**Before** mean ± SD range	 8 ±1.5 (6-11)	0.005*
	After **mean ± SD** **range**	 3.3±2.2 (1-7)	
Pain score	**Before** mean ± SD range	 2±0.7 (1-3)	0.004*
	After mean ± SD range	 0.4±0.52 (0-1)	

Keloids scores		Bleomycin (n=10)	p
Pruritus score	**Before** mean ± SD range	 1.6±0.84 (0-3)	0.006*
	After mean ± SD range	 0.2±0.42 (0-1)	

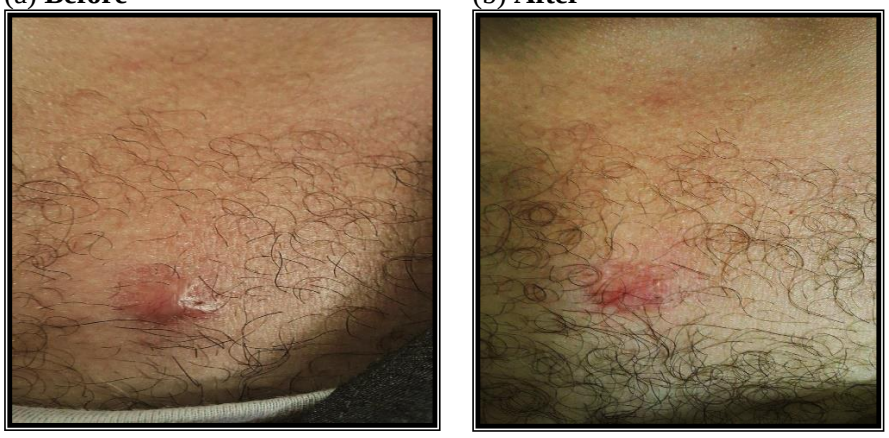
**Wilcoxon Signed Ranks Test *Statistically significant difference p<0.05

(a) **Before** (b) **After**

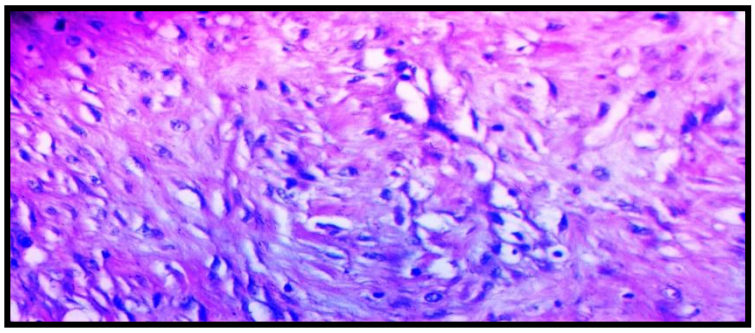


- **Figure (1)**
- (a) Before: Male patient 19 years with keloid in his right shoulder after trauma.
- (b) After: Keloid showed excellent degree of improvement after 6 sessions in the form of decrease in its height and size.

(a) **Before** (b) **After**



- **Figure (2)**
- (a) Before: Male patient 25 years old with keloid in his chest spontaneously developed.
- (b) After: Keloid showed excellent degree of improvement after 4 sessions in the form of flattening of keloid.



➢ **Figure (3):** histopathological evaluation before treatment, showing dense collagen bundles and fibroblasts disorganized in different directions separated by inflammatory cells (severe fibrosis). Collagen homogenization score = 3 (H&E × 400)

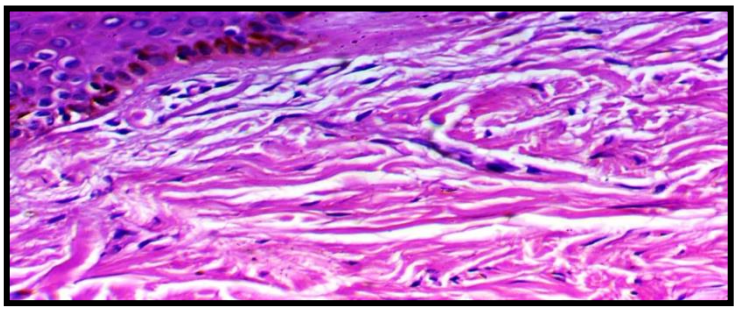


Figure (4): same case after treatment, showing thin short parallel collagen bands with absence of inflammatory cells (mild fibrosis) and basal layer hyperpigmentation. Collagen homogenization score = 1 (H&E × 400)

DISCUSSION

Keloid scars are fibro-proliferative lesions caused by abnormal wound healing and excess collagen deposition. Keloids can lead to severe functional impairment and psychological problems. They are very difficult to be treated and have high rate of recurrence [10].

There are multiple preparations that can be used intralesionally as a treatment option for keloid like triamcinolone acetonide, bleomycin and 5-fluorouracil. Triamcinolone acetonide is a traditional treatment therapy with proved efficacy. Bleomycin is one of the recent modalities for keloid management with comparable results to triamcinolone acetonide with minimal complications and less recurrence rate [11].

This study aimed to evaluate the efficacy and safety of intralesional injections of bleomycin in the treatment of keloids. A total of 10 patients with clinically diagnosed keloid lesions were enrolled in this study. Number of sessions ranged from (4-6) sessions with 2 weeks interval. Every patient was followed up for 5 months after the end of sessions to record any recurrence.

Age of the patients ranged from 15-25 years, which is consistent with the age range of keloid, as it is commonly seen in patients less than 30 years old [12]. As regards fitzpatrick's skin type, all patients had skin type 3 or 4. The incidence of keloid is about (3 – 20) times more in dark-skinned than in light-skinned people [13].

About 50% of patients in the present study reported burn as the cause of keloid. Burn is considered a main predisposing factor and cause of keloids, as it causes inflammation leading to increased and continuous collagen production by fibroblasts in the extracellular matrix [14]. This was in agreement with Salem et al [15] who reported burn as the cause of keloid in 40% of their patients, and in contrast to Payapvipapong et al [16] who reported burn as a cause of keloid in about 8% only of their patients.

In the present study intralesional bleomycin showed significant difference in Vancouver scar scale, pain and pruritus scores before and after treatment ($P<0.05$). According to grades of clinical improvement all patients showed degree of improvement ranged from moderate to excellent degrees.

This was better than Payapvipapong et al [16] who compared intralesional bleomycin (1 mg/mL) with intralesional TAC (10 mg/mL) for the treatment of keloids and hypertrophic scars with 38.1% improvement in bleomycin group. This difference can be explained by using a lower dose than we used (1.5 IU/ml).

Huu et al [17] conducted a study on 55 Vietnamese patients evaluating the effect of intralesional bleomycin in keloids treatment. Bleomycin was used with a concentration of 1.5 IU/ml monthly injected till improvement happened. At the end of their sessions, about 80.8% and 73.3% of patients recorded pruritus and pain relief, and 79.1% of

scars became fairly to completely flat. This was in agreement with the present study which showed 87.5% and 80% improvements in pruritus and pain scores respectively and showed good to excellent degree of improvement in 70% of patients.

Kabel et al [6] compared intralesional bleomycin and 5-fluorouracil in the treatment of keloids and hypertrophic scars, 60 patients were injected intralesionally with bleomycin at a concentration of 1.5 IU/ml with a maximum dose of 4 ml per session and two weeks interval. The mean total improvement according to Vancouver scar scale was 73% which is better than the present study (60%). This difference can be attributed to the larger number of patients included in their study giving a better chance for more included patients with good responsive keloids.

Histopathological examination of patients before treatment showed characters of keloids in the form of dense disorganized collagen bundles separated by aggregations of inflammatory cells. After treatment, the histopathological examination was consistent with the clinical results as collagen became more or less thin, parallel and arranged in the dermis with absence of inflammatory cells. (**Figures 3& 4)**

Mechanism of action of bleomycin depends on inhibition of DNA, RNA, and protein synthesis. It causes not only decrease in collagen synthesis, but also increase in its degradation [18]. In cultures of human dermal fibroblasts, there is highly significant reduction in lysyl oxidase concentration (an enzyme involved in collagen synthesis) as a result of the action of bleomycin. It also leads to keloid fibroblasts apoptosis [19].

In the present study reported side effects were tolerable including; pain during injection hyperpigmentation and recurrence with no systemic complications detected. All patients reported pain during injection ranged from mild to severe pain. Bleomycin can be classified as irritant drugs that can cause inflammation, pain, burning sensation and irritation at the injection site [20]. These results were in agreement with Kabel et al [6] & Huu et al [17] who reported pain during injection in almost 100% of their patients.

About 20 % of patients developed hyperpigmentation as a side effect in the present study. Most of our patients had darker skin types (Fitzpatrick skin types III and IV), in which post-inflammatory hyperpigmentation can easily develop [16]. This was in agreement with Huu et al [17] who reported hyperpigmentation in 56.7% of their patients. There are some other side effects that were reported in some studies like vesicles, bullae formation, ulceration, and skin atrophy, which weren't seen in our present study [6, 17].

According to patients' satisfaction levels, all patients reported degree of satisfaction ranged from moderate to excellent except for 1 patient. He was dissatisfied by the developed hyperpigmentation.

CONCLUSIONS

In conclusion, treatment of keloids is a challenging process. None of the available and newer modalities offers a permanent solution. The present study provided an evidence that intralesional bleomycin is effective and safe in the treatment of keloids. Further studies with larger number of patients and longer follow up periods are recommended.

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