An Evaluator-Blinded Pilot Study Comparing the Efficacy and Tolerability of Intralesional Bleomycin versus Intralesional Triamcinolone Scetonide in the Treatment of Small Keloids

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Background: In recent years, considerable interest has evolved over the use of chemotherapeutic agents for the treatment of scars. At present, there is currently no locally published trial comparing intralesional (IL) bleomycin and IL triamcinolone for the treatment of keloids.

Objective: This single center, pilot study aims to assess the efficacy and safety of IL bleomycin versus IL triamcinolone acetonide in the treatment of small keloids.

Methods: Six subjects aged 11 to 36 years old with two or more small keloids on the trunk or extremities were included in the study. A blinded evaluator assessed the study scars using the Vancouver Scar Scale (VSS) at the beginning and at the end of the trial period. The experimental keloid was injected with 0.1 mL of 1.5 U of bleomycin, while the control keloid was injected with 0.1 ml of 10 mg/mL of triamcinolone every 2 weeks. The incidence of adverse events, and self-assessed changes in pruritus, pain, erythema, softness, and size of the treated keloids were considered. Participant's satisfaction was also measured.

Results: The keloids that received IL bleomycin showed a significant improvement in the VSS at the end of the trial, which was not seen in the triamcinolone group. None of the patients were dissatisfied with the treatment outcomes. Adverse reactions were hyperpigmentation and crusting in the bleomycin group, and telangiectasia and hyperpigmentation for the triamcinolone group.

Conclusions: This pilot study shows that IL bleomycin is an effective and safe treatment for keloids. In addition to improving the cosmetic appearance of the keloids, it also improved pruritus and pain, and was perceived by the subjects as a satisfactory treatment. In addition, it may be used an alternative treatment for those non-responsive to IL triamcinolone. Larger and longer studies may follow this research to assess whether bleomycin could result in faster improvement and a prolonged time to recurrence, thereby resulting in fewer treatments over time.

Keywords: bleomycin, keloid, scar, triamcinolone acetonide

INTRODUCTION

Keloids are the result of abnormal wound healing responses, which lead to benign fibrous growths in predisposed individuals from certain ethnic groups[1]. Patients with keloids frequently seek consultation in dermatology clinics for aesthetic reasons. In addition, bothersome symptoms such as pain and pruritus are commonly reported. Functional disability may result from a large keloid, leading to difficulties in mobility and an adverse effect on one's activities of daily living. The negative impact that scars have on many individuals has prompted several researchers to continually seek prevention and treatment strategies. A review for the management of scars reveals the following armamentarium: scar revision surgery, compression therapy, topical silicone gel, laser therapy, radiation, corticosteroids, and other pharmacologic therapies, such as 5-fluorouracil, imiquimod 5% cream, onion extract, interferons, and immunotherapy, or a combination of these[2]. Success rates in clinical trials vary, mostly according to sample size, the length of study period, as well as the length of post-treatment surveillance. It is not uncommon for a dermatologist to be faced with a patient who has tried numerous therapeutic approaches, but without acceptable clinical response.

Among all the methods of treating keloids, perhaps the most accepted and most commonly used is IL triamcinolone acetonide, a corticosteroid. Its success in the treatment of scars lies in its ability to prevent excessive scarring by decreasing collagen synthesis, glycosaminoglycan synthesis, the proliferation of fibroblasts, and by downgrading the expression of inflammatory mediators[3]. Although success rates are pegged at 50% to 100%, the rate of recurrence of keloids after treatment ranges from 9% to as high as 50%[4]. Unfortunately, effective treatment is not guaranteed and typically requires many sessions Side effects include the pain of the injections, thinning and at-rophy of the skin and subcutaneous tissues, the development of steroid acne, capillary dilation, and hypopigmentation[5]. These concerns have led the investigators to look for an alternative treatment that will result in less recurrence and better outcomes in a shorter period of time.

In recent years, considerable interest has evolved over the use of chemotherapeutic agents for the treatment of keloids. Bleomycin is an antitumor, antibacterial, and antiviral agent that was first isolated in 1962 by Umezawa and colleagues from the actinomycotic soil fungus *Streptomyces verticillus*. This drug is most commonly used as a chemotherapeutic agent in the treatment of various kinds of malignancy such as squamous cell carcinoma of the head and neck, skin, penis, cervix, vulva, lymphoma, testicular carcinoma, and in malignant pleural effusion. In the field of dermatology, there are currently no approved United States Food and Drug Administration (US FDA) indications for the use of IL bleomycin. Its off-label use for dermatologic diseases however, is quite common, and includes treatment for tumors, vascular anomalies, cutaneous malignancies, and verruca[6].

In 1996, the first clinical trial using IL bleomycin as therapy for scars was published. The researchers, Bodokh and Brun[7], administered three to five IL injections of bleomycin to 5 hypertrophic scars and 31 keloids within a period of one month. Complete regression of the scars was seen in 69.4% of patients. These promising results prompted a more recent study done by España et al[8]. In their trial, 1.5 IU/mL of bleomycin was drizzled onto the scars of 13 patients. Using a 25-gauge needle, the medication was introduced into the skin via a multiple-puncture method, where 40 punctures/ 5 mm^2 was given. After approximately 1 to 5 sessions spanning 1 to 4 months, primary outcome measures (size, symptomatic improvement, color, and thickness of the scars) were measured. 53.8% of patients had complete flattening of their lesions; 38.4% had highly significant flattening, and the remaining 1 patient had significant flattening.

To the best of the authors' knowledge, there is currently no locally published trial comparing IL bleomycin and IL triamcinolone for the treatment of small keloids.

OBJECTIVES

General Objectives:

1. To assess the efficacy of IL bleomycin in the treatment of keloids.
2. To evaluate the safety of IL bleomycin in the treatment of keloids.
3. To determine the tolerability of IL bleomycin in the treatment of keloids by examining the subjects' post-treatment satisfaction.

Specific Objectives:

1. To compare changes in the vascularity, pigmentation, pliability, and height between the control lesion (triamcinolone) versus the experimental lesion (bleomycin) using the VSS.
2. To determine the incidence of adverse events related to both groups.

METHODOLOGY

Study Design

This was an 8-week, left-right comparison study on subjects with 2 or more small keloids.

Patient Selection and Randomization

Subjects were recruited from May to July 2011 from the outpatient department of the Department of Dermatology, Jose R. Reyes Memorial Medical Center, Sta. Cruz, Manila, Philippines. Those with known allergies to components of triamcinolone acetonide or bleomycin, pregnant women, lactating mothers, subjects with active comorbid illnesses, and those incapable of giving a written informed consent were excluded from the study. A total of six participants aged 11 to 36 years old with two or more keloids measuring not more than 2 cm^3 on the trunk or extremities were included in the study.

Personal data forms were collected regarding their sex, age, occupation, cause of the keloid, site, length of time the keloids have been present, associated symptoms, and any previous treatments for their scars. Toss coin method was used to determine which of the subject's keloid received bleomycin or triamcinolone.

The study was approved by the Institutional Review Board of the said institution and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent from the patients and/or guardians was obtained before the start of the trial.

Treatments and Evaluations

Bleomycin sulfate (Bloicin-S) 15 IU/mL was dissolved in 10 mL of 2% lidocaine to make a concentration of 1.5 IU/mL. The area of the first keloid (experimental lesion) was given IL bleomycin 0.1 mL while 0.1 mL triamcinolone (Kanolone) 10 mg/mL was given to the area of the 2^{nd} keloid (control lesion). Sessions were repeated every 2 weeks for 2 months, for a total of 4 sessions.

An evaluator assessed the scars using the VSS at the beginning and at the end of the study. The VSS is an evaluator-based scale that measures four scar parameters: pigmentation, vascularity, pliability, and height (Table 1). Photographs were taken at baseline and at each visit using a digital camera (Panasonic Lumix LX3). Any adverse events were recorded.

At the end of the study period, participants were asked to answer a questionnaire regarding subjective changes in the following symptoms: pain, pruritus, erythema, pliability, and scar size, whether these improved (I), worsened (W), did not change (NC), or was not present (NA). Overall satisfaction was also measured using a 5-point Likert scale, where: 1 (dissatisfied), 2 (somewhat dissatisfied); 3 (neither satisfied nor dissatisfied); 4 (somewhat satisfied); and 5 (very satisfied).

Table 1. Vancouver Scar Scale

Score	Pigmentation	Vascularity	Pliability	Height
0	Normal (Closely resembles the color of nearby skin)	Normal	Normal	Normal (Flat)
1	Hypopigmentation	Pink (Slight increase in local blood supply	Supple (Flexible with minimal resistance)	<2 mm
2	Hyperpigmentation	Red (Significant increase in local blood supply)	Yielding (Giving way to pressure, offering moderate resistance, but does not behave as a solid scar mass)	>2 & <5 mm
3	-	Purple (Excessive local blood supply)	Firm (Solid/inflexible unit, not easily moved, resistant to manual pressure)	>5 mm
4	-		Banding Rope-like tissue that blanches with extension of scar but does not limit range of motion)	-
5			Contracture (Permanent shortening of scar producing deformity or distortion; limits range of motion	

Statistical Methods

Data were analyzed using the Mann-Whitney U test and Pearson's chi-squared test. A level of significance of 5% was adopted.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 6 subjects were included in the study. Table 2 shows a summary.

Table 2. Patient demographics and scar characteristics

Subject	Age	Sex	Occupation	Scar Age	Location	Cause	Symptoms	Prior Treatment
1	36	M	Logistic officer	< 1 yr	Foot/Arm	Trauma	Pruritus, erythema	None
2	23	M	Promodizer	> 1yr	Chest	Trauma	Pruritus, erythema	None
3	23	M	Loans Assistant	> 1 yr	Chest	Acne	Pruritus, erythema	None
4	11	F	Student	< 1 yr	Chest/Shoulder	Varicella	Pruritus, erythema	None
5	15	M	Student	> 1 yr	Back	Varicella	Erythema	IL steroid
6	27	M	Writer/researcher	> 1 yr	Chest	Acne	Pruritus, Pain, increasing size, erythema	IL steroid Topical allantoin gels

Assessment of Scar Height, Vascularity, Pigmentation and Pliability using the VSS

The total VSS for the studied keloids were recorded at baseline and at the end of the trial (Table 3). Results show that for the bleomycin group, there was a significant improvement in the VSS (p = 0.05), whereas no statistically significant improvement was seen in the triamcinolone group (p = 0.34). The results also show that there were no statistically significant changes in the individual parameters of height, vascularity, pigmentation, and pliability.

Table 3. Comparison of initial and final total VSS scores

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	9	7	4	3
2	7	4	8	4
3	9	7	9	8
4	7	4	3	0
5	6	6	6	7
6	7	4	9	7
Mean	7.5 ±1.2	5.3 ± 1.5	6.5 ± 2.6	4.8± 3.1
z score	**1.92**		0.96	
p-value	**0.05**		0.34	

Table 4. Height scores of the keloids before and after treatment

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	3	2	0	0
2	3	1	3	1
3	2	2	2	2
4	1	0	0	0
5	0	2	1	2
6	2	1	2	2
z score	0.80		0.16	
p-value	0.42		0.87	

Table 6. Pigmentation scores of the keloids before and after treatment

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	2	2	2	2
2	2	1	2	1
3	2	2	2	2
4	0	2	0	0
5	1	1	0	2
6	2	2	2	2
z score	-0.08		-0.08	
p-value	0.93		0.94	

Table 7. Pliability scores of the keloids before and after treatment

	Bleomycin		Triamcinolone	
Subject	**Initial**	**Final**	**Initial**	**Final**
1	3	2	1	1
2	1	1	2	1
3	3	2	3	3
4	3	1	0	0
5	3	1	3	1
6	1	1	3	2
z score	1.52		0.88	
p-value	0.12		0.38	

Subject's Self-Assessment

At the end of the study period, participants were asked to answer a self-assessment survey regarding changes in pruritus, pain, erythema, softness, and size. Although not statistically significant, all patients reported an improvement in the softness and size of the keloid that was treated with bleomycin. The single patient who reported keloid pain reported this pain to have improved with the bleomycin treatment. Only 1 subject reported a worsening of erythema, and only 1 noted no change in pruritus after bleomycin treatment (Table 8).

Subjects were also asked to grade their satisfaction with the treatments they received (Table 9). None of the patients were dissatisfied with the treatment outcome. Mean satisfaction for the bleomycin treatment was lower than the triamcinolone treatment. There was no significant difference in satisfaction between these two (p = 0.55).

Table 1. Vancouver Scar Scale

Subject	Pruritus		Pain		Erythema		Softness		Size	
	Bleo	**Triam**	**Bleo**	**Triam**	**Bleo**	**Triam**	**Bleo**	**Triam**	**Bleo**	**Triam**
1	NC	NC	NA	NA	W	W	I	NC	I	I
2	I	I	NA	NA	I	W	I	I	I	I
3	I	I	NA	NA	I	I	I	I	I	I
4	I	I	NA	NA	I	I	I	I	I	I
5	NA	NA	NA	NA	I	NC	I	I	W	I
6	I	I	I	NA	I	I	I	I	I	I
Total improved	4/6	4/6	1/6	0/6	5/6	3/6	**6/6**	5/6	**6/6**	5/6

Bleo, bleomycin; Triam, triamcinolone; NC, no change; NA, not present; W, worsened; I, improved

Table 9. Subject satisfaction with end result of the treatments

Subject	Bleomycin	Triamcinolone
1	4	4
2	3	3
3	3	3
4	5	5
5	4	5
6	3	4
mean	**3.6 ± 0.81**	**4 ± 0.89**
p-value	0.55	

Adverse Reactions

For the keloids that were given triamcinolone, 1 subject exhibited telangiectasia and another had hyperpigmentation. In the bleomycin group, 1 subject showed both hyperpigmentation and minimal crusting at the injection site of the treated area.

DISCUSSION

Disfiguring and bothersome keloids are one of the most common reasons for consultation in dermatology clinics. The general consensus on the guidelines for the management of these scars is through a multi-modality approach, where IL triamcinolone as a first-line treatment for scars has been well established. A study done by Anthony et al comparing different strengths of triamcinolone concluded that a dosage of 10 mg/mL followed by 40 mg/mL was most effective, with the lowest recurrence rate[8]. Furthermore, studies suggest that treatment periods of as long as 4 – 6 months are needed before any noticeable improvement can be observed. Because of these drawbacks, recent studies using IL bleomycin have been done to assess its efficacy in the treatment of keloids. Although its exact mechanism remains unknown, recent experimentation on cultures of human dermal fibroblasts have found that bleomycin directly inhibits the formation of collagen of these cells. It has also been postulated that bleomycin has the capability to reduce the levels of lysyl-oxidase, the cross linking enzyme involved in collagen maturation[9].

In the present investigation, the initial VSS of the scars in the triamcinolone group did not statistically improve, while VSS of the scars that received IL bleomycin did. This result suggests that bleomycin has the potential to be a successful alternative in patients not responsive to the usual therapy with triamcinolone.

The present study parallels earlier studies done where bleomycin was effective in decreasing scar size. Saray and Gülec[10] investigated a different method of introducing bleomycin into scars in 2005 when they applied intralesional dermojet injections of the drug to 14 patients who were unresponsive to intralesional steroid injection in the past. 0.1 mL of 1.5 IU/mL bleomycin was injected 0.5 mm apart into each lesion in sessions that were repeated monthly. Measurements of scar height, scar pliability, and erythema were taken during the treatment and follow-up periods. The results showed that 73.3% of lesions showed complete flattening, 6.7% showed highly significant flattening, 13.3% had significant flattening, and only 6.7% moderate flattening. Mean scar height was significantly lower, and both the mean scar pliability as well as erythema scores were significantly better at the end of the treatment period.

The participant's self-assessment is also integral to any study on keloid treatment. Statistics of the present study revealed that there was no significant difference in the patients' self-assessments between the bleomycin and triamcinolone groups. It appears patients considered both drugs as equally effective in improving the appearance of the scars and their associated symptoms. Interestingly, the subjects' satisfaction did not parallel the objective findings – although bleomycin contributed to better results, the satisfaction means were higher in the triamcinolone group. Perhaps other factors (such as pain from the procedure) made bleomycin less desirable than triamcinolone.

Adverse effects observed with bleomycin were hyperpigmentation of the treatment site and minimal hemorrhagic crusting, which may have been due to the effect of bleomycin or due to scratching of the patient. The crusting resolved spontaneously within a week. As for triamcinolone, 1 patient was observed to have telangiectasia and another had slight hyperpigmentation of the lesion. The present study did not assess for systemic adverse effects of the drug, since these types of problems are seen usually in intravenous usage of much higher concentrations, i.e. 150 mg, of the drug[6]. In previous studies using similar concentrations, no systemic toxicity has been reported.

Limitations of the Study

Measuring keloid height and surface area are often challenging in keloid studies due to the irregular shapes of these scars. Gradated measuring devices, like rulers and calipers, are prone to intra-observer variability. To this end, the most precise and accurate means of measuring scar height at present is through ultrasonography[10], while planimetry by digital photography has been recommended as the standard of choice for measuring surface area[11]. Color evaluations may benefit from the use of certain tools (e.g. laser-Doppler flowmeter, etc.), but these were not accessible to the investigators.

This pilot study encourages trials with a bigger sample size, with a uniform location of keloids, with a longer study period, and that includes medium to large keloids, in order to assess time to improvement and rate of recurrence when using IL bleomycin for the treatment of keloids.

CONCLUSIONS

The results of the present study are promising - we can conclude that IL bleomycin is an effective and safe treatment for keloids. Scar height, pigmentation, vascularity, and pliability of scars showed a decreasing trend, approaching the appearance of normal skin. Subjects were generally satisfied with the outcome, and adverse events were mild, cutaneous in nature, and resolved spontaneously. The present study also suggests that IL bleomycin may be used an alternative treatment for those who have a slow response or are non-responsive to IL triamcinolone.

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