Original article

Comparative study between intralesional injection of bleomycin and 5-fluorouracil in the treatment of keloids and hypertrophic scars

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Abstract

The aim of this work was to evaluate the efficacy and safety of intralesional injection of 5-fluorouracil and bleomycin in the treatment of keloids and hypertrophic scars. One hundred and twenty patients were divided into the following groups: group IA was injected intralesionally with 5-fluorouracil; group IB was injected intralesionally with a combination of triamcinolone acetonide and 5-fluorouracil; group II was injected intralesionally with bleomycin. Patients underwent follow up by photographing and Vancouver scar scale system. There was a significant improvement in the Vancouver scar scale in group II compared to group I after treatment. There was hyperpigmentation, pain and ulceration in all the studied groups. Pain was significantly decreased in group IB compared to that in group IA, ulceration was significantly decreased in group II than in group I while pain after injection was increased in group II than in group I. Relapse occurred in 12 patients of group IA, 14 patients of group IB and no relapse occurred in group II. So, intralesional injection of bleomycin was more effective and better in remission than intralesional 5-fluorouracil injection in the treatment of keloids and hypertrophic scars regardless of patient’s age, sex, disease duration or site of the lesion.

Keywords: Bleomycin; Fluorouracil; Keloids; Hypertrophic scars

1. Introduction

Keloids and hypertrophic scars are characterized by excessive deposition of dermal collagen with resultant scar tissue. A keloid scar is benign, non-contagious and sometimes accompanied by severe itching, sharp pains and changes in texture. In severe cases, it can affect movement of skin and may ulcerate. The probability of recurrence of keloids after surgical removal is high, usually greater than 50% (Hunasgi et al., 2013; Maghrabi and Kabel, 2014).

Five-Fluorouracil (5-FU) is a pyrimidine analog, which is used in the treatment of cancer. It is also used in ophthalmic surgery, specifically to augment trabeculectomy in patients deemed to be at high risk for failure. 5-FU acts as an anti-scarring agent in this regard, since excessive scarring at the trabeculectomy site is the main cause for failure of the surgery (Rothman et al., 2000). Recent trials have
used 5-FU topically for treating hypertrophic scars and some types of basal cell carcinomas of the skin. Some studies had used 5-FU intraleisonally in the treatment of keloids and hypertrophic scars alone or mixed with triamcinolone acetonide (TAC). The latter is thought to decrease pain and inflammation (Davison et al., 2009).

Bleomycin is a glycopeptide antibiotic that is widely used as an anti-cancer agent. The drug is used in the treatment of Hodgkin lymphoma, squamous cell carcinomas and testicular cancer, as well as in the treatment of plantar warts (Lewis and Nydorf, 2006). Also, bleomycin has been tried intraleisonally to treat keloids and hypertrophic scars. The commonest complication of bleomycin injection was hyperpigmentation, which was seen in 75% of patients (Saray and Gülec, 2005). This work was a trial to evaluate the efficacy and safety of intraleisonal injection of 5-fluorouracil and bleomycin in the treatment of keloids and hypertrophic scars.

2. Methods

2.1. Location

This study was conducted at dermatology, venereology and andrology department, faculty of medicine, Benha University, Egypt. This study was approved by the Research Ethics Board at Benha University. This work complied with the principles laid down in the Declaration of Helsinki.

2.2. Study design

2.2.1. Equipments

- A 1 ml insulin syringe with a fixed 30 gauge needle.
- Mepivacaine HCl 3% (Mepivacaine ampoule, Alexandria Pharmaceutical Co., Egypt).
- Five-fluorouracil (Fluorouracil 250 mg ampoule, Biosynthesis Pharmaceutical Co., Egypt).
- Bleomycin (Bleocip 15 mg vial, Cipla Co. Ltd, Verna industrial state, Goa, India).
- Triamcinolone acetonide (Kenacort vial, Bristol-Myers Squibb).

This study was conducted on one hundred and twenty patients with keloids and hypertrophic scars of varying sizes and durations selected from the Dermatology and Andrology outpatient clinic of faculty of medicine, Benha University, Egypt.

2.2.2. Inclusion criteria

A minimum age of 15 years, acceptable pretreatment laboratory studies (complete blood cell count, serum chemistries, urine analysis, and pregnancy test) and a written consent was taken from each patient before the study.

2.2.3. Exclusion criteria

- Pregnancy, lactation, chronic renal failure and any abnormalities of liver function tests or complete blood count.

2.2.4. Groups

The patients were divided into the following groups:

- Group (IA): included thirty patients who were injected intraleisonally with 5-FU at a concentration of 50 mg/ml. Initially, local anesthetic Mepivacaine HCl 3% was administered at the lesion site. Then, the patients were injected intraleisonally with 5-fluorouracil at a concentration of 50 mg/ml, multiple injections were given at 1 cm intervals on average, 0.2–0.4 ml/cm². The maximum dose was 2 ml per session with a two week interval (Kontochristopoulos et al., 2005).

- Group (IB): included thirty patients who were injected intraleisonally with a mixture of 0.1 ml of 40 mg/ml TAC and 0.9 ml of 5-FU (50 mg/ml). Initially, local anesthetic (Mepivacaine HCl 3%) was administered at the lesion site. Then, the patients were injected intraleisonally with a mixture of 0.1 ml of 40 mg/ml triamcinolone acetonide and 0.9 ml of 5-FU (50 mg/ml), multiple injections were given at 1 cm intervals on average, 0.2–0.4 ml/cm². The maximum dose was 2 ml per session with a two week interval (Asilian et al., 2006).

- Group (II): included sixty patients who were injected intraleisonally with bleomycin at a concentration of 1.5 IU/ml. Initially, local anesthetic (Mepivacaine HCl 3%) was administered at the lesion site. Then, multiple intraleisonal injections of bleomycin at a dose of 0.5–1 ml/cm² with a maximum dose of 4 ml per session using insulin syringe were administered with a two week interval (España et al., 2001).

All patients were subjected to complete history taking and dermatological examination included site, size, shape, color and consistency of the lesion. Investigations into blood count, liver and kidney functions were done before treatment and then at a monthly interval during therapy. The patients were informed about the nature of each procedure, expected number of treatments and also expected side effects of the procedure. Follow up of the patients was performed by the Vancouver scar scale system after stopping the treatment for 12 months.

2.3. Assessment of the clinical response

Assessment of keloids was done at the beginning of the treatment, at 4, 8, and 12 weeks, and during the follow up period. The assessment included clinical changes in the keloids by photographs and by reporting any side effects that the patients experienced. Clinical assessment was carried out using Vancouver scar scale that includes vascularity, pigmentation, pliability and height. The results were recorded from (0) to (14) where (0) reflected normal skin (Baryza and Baryza, 1995). The clinical improvement was
judged on the basis of a decrease in vascularity, pigmentation and height as well as softening of the scar and improvement of symptoms.

2.4. Statistical analysis

Data were presented as mean ± standard deviation (SD). An ANOVA and Student’s t-test were used for evaluating the statistical significance of differences in means. Pearson’s correlation coefficient ($r$) was applied to correlate between the parameters. A $P$ value of less than 0.05 was considered to be statistically significant.

3. Results

The ages of the patients ranged from 16 to 54 years with mean values of (29.87), (32.07) and (31.5) in group (IA), (IB) and (II) respectively. The duration of the lesions ranged from 4 months to 23 months. The most commonly affected sites were chest, shoulder, back, forearm and neck.

3.1. Number of sessions required for patient groups

In group IA, the numbers of intralesional injections of 5-FU received ranged from 4 to 6 sessions. In group IB, the numbers of intralesional injections of 5-FU mixed with TAC ranged from 5 to 6 sessions. In group II, the numbers of intralesional injections of bleomycin received ranged from 2 to 6 sessions. The difference was statistically significant compared to that of group I (IA and group IB). This means that bleomycin is more effective than 5FU alone or mixed with TAC (Fig. 1).

3.2. Vancouver scar scale in the studied groups

In group IA, the mean Vancouver scar scale in all patients before treatment was $9.67 \pm 1.35$ and it was $4.47 \pm 1.3$ after treatment with a mean total improvement of 54%. In group IB, the mean Vancouver scar scale in all patients before treatment was $9.67 \pm 1.63$ and it was $4.46 \pm 1.55$ after treatment with a mean total improvement of 55%. In group II, the mean Vancouver scar scale in all patients before treatment was $9.32 \pm 1.46$ and it was $2.7 \pm 0.95$ after treatment with a mean total improvement of 73%. The mean value of group II after treatment was statistically significant compared to that of group I after treatment (Figs. 2–5).

3.3. Correlation between age, sex, disease duration and clinical response

There was no correlation between age, sex, disease duration and clinical response in all groups (Table 1).
3.4. Side effects in the studied groups

Regarding side effects, there was hyperpigmentation, pain and ulceration in all the studied groups. However, pain was significantly decreased in group IB compared to group IA, ulceration was significantly decreased in group II than in group I, while pain after injection was increased in group II than in group I (Fig. 6).

3.5. Relapse in the studied groups

Regarding relapse, there was relapse in 12 patients (40%) of group IA, in 14 patients (46.67%) of group IB and no relapse occurred in any patients of group II (Table 2).

4. Discussion

Keloids and hypertrophic scars are fibrotic conditions that represent a model of altered wound healing with overproduction of extracellular matrix and marked proliferation of fibroblasts. Their exact etiology and pathophysiology is still poorly understood. No single
In the present study, intralesional injection of 5-FU resulted in a significant improvement in vascularity, pliability and height while worsening in the pigmentation. The improvement was more than 50% in the majority of the patients. Also, the results of the present study were in agreement with those of a study by Asilian et al. (2006) in which 69 patients of keloids and hypertrophic scars were randomly assigned into three groups. In one group, intralesional TAC was used, in the second intralesional TAC+5-FU was used, in the third TAC+5-FU injections were followed by pulsed-dye laser. All groups showed an acceptable improvement in nearly all measures, but in comparison between groups, there was a statistically more significant improvement in the TAC+5-FU and TAC+5-FU + PDL groups. Also, Darougheh et al. (2007) had given a combination of intralesional TAC and 5-FU to twenty patients with keloids and hypertrophic scars at weekly intervals for 8 weeks. A good to excellent improvement was reported by 55% of the patients as evidenced by an acceptable improvement in nearly all parameters except pruritus and percentage of itching reduction.

In the present study, multiple intralesional injections of bleomycin produced a significant improvement in vascularity, pliability and height while worsening pigmentation compared to 5-FU injection. These results were in agreement with those of Saray and Gülec (2005) who used dermoejet injection of bleomycin to treat 14 patients with keloids and hypertrophic scars that had not responded to intralesional injection of TAC. 73% of the lesions showed complete flattening, 7% showed highly significant flattening, 13% showed significant flattening and 7% showed moderate flattening.

Espana et al. (2001) used intralesional bleomycin injection to treat keloids and hypertrophic scars in 13 patients using multiple puncture method. The dose applied was 2 ml/cm² with a maximum of 6 ml per session. Complete flattening was seen in 6 patients, highly significant flattening (>90%) was observed in 6 patients, and significant flattening (75–90%) in 1 patient. Also, Aggarwal et al. (2008) used bleomycin by multiple superficial puncture technique to treat fifty patients with keloids and hypertrophic scars. Three applications were given at an interval of fifteen days followed by a fourth and final application two months after the last application. This resulted in complete flattening in 22 patients (44%), significant flattening in 11 patients (22%), adequate flattening in 7 patients (14%) and no flattening in 10 patients (20%). The difference between the present study and that of Aggarwal et al. (2008) may be due to the difference in the methods of injection. It could be
concluded that intralesional injection of bleomycin is more effective than the superficial puncture techniques.

Naenini et al. (2006) treated 45 patients with keloids and hypertrophic scars. They were divided into two groups; group A was treated by bleomycin tattoo, group B was treated with cryotherapy combined with intralesional TAC. They were given four therapeutic sessions at a one-month interval. Therapeutic response in lesions less than 100 mm² was higher than 88% in both groups but in larger lesions, the response to bleomycin was significantly better than cryotherapy combined with TAC.

In the present study, there was recurrence during the follow-up period in 12 (40%) patients of group IA and in 14 (46.67%) patients of group IB. These results were in agreement with those of Kontochristopoulos et al. (2005) who noted recurrence in 47% of patients who responded to treatment within 1 year. However, Nanda and Reddy (2004) observed no recurrence of symptoms or the lesion during the follow-up period of 24 weeks in any of the patients.

In group II, there was no recurrence during the follow-up period. This was in agreement with that of Saray and Gülec (2005) who followed up their patients for 19 months after treatment and observed no recurrence of the lesions. Also, Bodokh and Brun (1996) used bleomycin infiltration and observed no recurrence in any patients. On the other hand, España et al. (2001) observed recurrence in 15% of patients 10 months after the last infiltration of bleomycin.

In the present study, no correlation between clinical response and age, sex or duration of keloids was found. This was in line with that of Nanda and Reddy (2004) who observed no correlation between duration of keloid and response to treatment. Also, Naenini et al. (2006) found no correlation between location or duration of lesions and the therapeutic response. On the contrary, Kontochristopoulos et al. (2005) found a correlation between duration of keloids and recurrence. He observed that the response was low in older lesions.

Regarding the side effects in the present study, there were hyperpigmentation, ulceration and pain. In group IA, hyperpigmentation was present in 20 patients (66.67%), ulceration was present in 18 patients (60%) and pain at the injection site was present in 10 patients (33.33%). The side effects in group IB were nearly the same as group IA except for pain which was significantly decreased in group IB. In a study by Darougheh et al. (2007), no adverse effects were seen in the TAC+5-FU group. In group II of the present study, hyperpigmentation was present in 42 patients (70%), ulceration was present in 14 patients (21.33%) and pain at the injection site was present in all patients (100%).

In a study by España et al. (2001), four patients had skin type II and nine patients had skin type III. They detected slight residual hyperpigmentation in two patients with skin type III. In the present study, all patients had skin types III, IV and V. The difference between the present study and that of España et al. (2001) may be due to the difference in skin types of patients in the two studies.

In conclusion, intralesional injection of bleomycin was more effective and better in remission than intralesional 5-FU injection in the treatment of keloids and hypertrophic scars regardless of patient’s age, sex, disease duration or site of lesion.

Conflict of interest

None of the authors have a conflict of interest to report.

References


