

Efficacy of Intralesion Injection of Combined 5-Flourouracil and Triamcinolone Versus Triamcinalone Alone in Keloids and Hypertrophic Scars: A Comparative Analysis

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ABSTRACT

Objective: The treatment of keloids and hypertrophic scars is challenging and controversial. The therapeutic agents found in literature include silicone sheets, compression garments, corticosteroid injections, 5-fluorouracil (5-FU), bleomycin and interferon, topical imiquimod, cryotherapy, radiation, and laser or light-based therapies. Triamcinolone acetonide (TCA), a corticosteroid, considered first line treatment for the prevention and the treatment of keloids and hypertrophic scars. To compare the efficacy of triamcinolone acetonide alone and triamcinolone acetonide plus 5-florouracil for treating keloids and hypertrophic scars in burn patients.

Methodology: Patients were divided into two groups A and B on the basis of treatment regimen i.e. Group A (TCA alone) and Group B (5FU+TCA). Efficacy of both treatments were compared for improvement in Vancouver scar scale (VSS) and pruritus scale.

Results: Mean VSS score pretreatment was calculated as 10.74±2.36 in Group-A and 10.27±3.14 in Group-B. Post treatment it was reduced to 5.58±1.04 in Group-A and 3.41±2.11 in Group-B. Comparison of efficacy shows improvement of 65.80% in Group-A and 75.07% in Group-B, p value was 0.047 showing a significant difference.

Conclusion: Combination therapy of intra-lesion injection of triamcinolone acetonide and 5-florouracil has significantly higher efficacy as compared to triamcinolone acetonide alone for the treatment of keloids and hypertrophic scars, however, necessary precautions have to be taken.

Keywords: Keloids, hypertrophic scars, triamcinolone acetonide, 5-florouracil, efficacy, Vancouver scar scale.

Authors' Contribution:

^{1,2,3}Conception; *Literature research; manuscript design and drafting*, ^{4,5,6}Critical analysis and manuscript review; ^{7,8,9}Data analysis; *Manuscript Editing*.

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Introduction

Keloid and hypertrophic scars are dermal fibroproliferative disorders that result from abnormal wound healing in response to skin trauma or inflammation.¹ They are characterized by unregulated growth with excessive collagen

formation and can be cosmetically and functionally unsettling to the patients.² Keloids and hypertrophic scars may be symptomless, however, they can be associated with pain, itching, hyperesthesia, pruritus, movement restrictions and cosmetic disfigurement.³ Dark skinned individuals of African, Asian, and Hispanic descent have higher rates of

keloid development compared to Caucasians. The incidence in these darker-pigmented populations' ranges from 4.5% to 16%.⁴ Abnormal prolongation of the inflammatory phase of wound healing can lead to an imbalance in the destruction and deposition of extracellular matrix, which results in accumulation of collagen and other ECM components. The flood of ECM components in the dermis and surrounding subcutaneous tissue leads to excessive scarring and keloid formation.⁵ Keloid and hypertrophic scarring are differentiated on the bases of extent of lesion and duration, with former extending beyond the initial scar and duration more than 1 year. Whereas hypertrophic scarring is confined to initial scar and its duration is less than 1 year. The treatment of keloids and hypertrophic scars is challenging and controversial. The therapeutic agents found in literature include silicone sheets, compression garments, intra lesion corticosteroid injections, 5-fluorouracil (5-FU), bleomycin and 4 interferon, topical imiquimod, cryotherapy, radiation, and laser or light-based therapies.⁶ Intra lesion injection of corticosteroid is used as the first line treatment for the prevention and treatment of keloids and hypertrophic scars. The function of corticosteroids is to inhibit the inflammatory cell migration, induce vasoconstriction and suppress the proliferation of fibroblasts, especially at high doses of the drug.⁷ Intra lesion injection of Triamcinolone acetonide (TCA), a corticosteroid is used as 1st line agent. The use of a single agent has a very high percentage of failure therefore, there are many tested combinations that can be used in order to achieve a more positive result, especially a lower recurrence rate.⁸ Combination of 5-FU and corticosteroid has been proposed in literature. 5FU (5-florouracil) is a chemotherapeutic drug which resists proliferation of fibroblast in tissue cultures. It is hypothesized that it can lessen post-operative scar formation due to this property.⁹

Current practice in our hospital is intralesional TCA but as recent studies showed that combined therapy with 5FU and TCA is more effective than TCA

monotherapy, combination therapy is evaluated in this study. The study compared intra lesion injection of the combination of TCA and 5-FU with intra lesion injection of TCA alone. VSS¹⁰ and pruritus scale¹¹ were used for comparison. (Table No. 1 and Table No. 2). Our study evaluated that if the findings of other studies are applicable to the population which presents to our setup that are mostly from northern Punjab, Khyber Pakhtunkhwa, Azad Jammu Kashmir and Gilgit Baltistan. As very few studies are available that compare the combination therapy with TCA alone. This study will be a valuable addition to the literature and can be the guide for future studies.

Methodology

It was a randomized controlled trial conducted at the Department of Plastic Surgery, Fauji Foundation Hospital, Rawalpindi. The patients were divided into two groups. Group A consisted of patients who underwent the treatment of hypertrophic scar or keloid by intra lesion injection of TCA alone. TCA 10mg (0.25ml of 40mg/ml TCA diluted with 0.75ml injectable normal saline) was administered once every 2 weeks for a maximum of six sessions. Group B patients had intra lesion injection of combination of TCA and 5-FU. TCA 4mg (0.1ml of 40 mg/ml TCA) mixed with 5-FU 45mg (0.9ml of 50 mg/ml 5-FU) was administered once every 2 weeks for a maximum of six sessions. The sample size was 90 with 45 in each group, which was calculated by using WHO sample size calculator (2.2b).

Sampling was done by non-probability convenient sampling. All the patients presenting with keloids and hypertrophic scars were included in the study except pregnant or lactating mothers, patients who were already taking systemic steroids as confirmed through clinical record, patients who received treatment for keloids or hypertrophic scar in the past 12 months, patients with active inflammation, infection or ulcer in or around the keloid or hypertrophic scar and patients

Table 1: VANCOUVER SCAR SCALE	
Scar Characteristic & Score	Description
Pigmentation	
0	Normal color that closely resembles the color over the rest of one's body.
1	Hypopigmentation.
2	Hyperpigmentation.
Vascularity	
0	Normal color that closely resembles the color over the rest of one's body.
1	Pink
2	Red
3	Purple
Pliability	
0	Normal
1	Supple: flexible with minimum resistance.
2	Yielding: giving way to pressure.
3	Firm: inflexible not easily moved, resistant to manual pressure.
4	Banding: rope like tissue that blanches with extension of scar.
5	Contracture: permanent shortening of scar producing deformity or distortion.
Height	
0	Normal
1	<2mm (as assessed on common scale having "mm" marks)
2	<5mm
3	>5mm

with any other comorbidities. After ethical clearance and consent of patients, they were enrolled in study. Efficacy of both treatments were compared by VSS score (lower score is considered better) and pruritus scale after 4 weeks of completion of treatment, also

number of sessions required to reach at least 50% of reduction in VSS were compared in both groups. Patients were reviewed at each session and after 4 weeks of completion of treatment. Efficacy was compared in both groups by applying chi square test and p value of ≤ 0.05 was considered significant.

Results

A total of 90 cases (45 in each group) were enrolled in this study. Mean age distribution in group A was 35.38 years (± 9.27) and in Group-B, it was 34.09 years (± 9.29). Gender distribution shows that 64.44% in Group-A and 66.67% in Group-B were males while 35.56% in Group-A and 33.33% in Group-B were females. Mean scar size in Group-A was 6.8cm ± 2.65 cm and 7.45cm ± 2.93 in Group-B. (Table No. 3)

Mean VSS score pretreatment was calculated as 10.74 ± 2.36 in Group-A and 10.27 ± 3.14 in Group-B. Post treatment was reduced to 5.58 ± 1.04 in Group-A and 3.41 ± 2.11 in Group-B. Comparison of efficacy shows improvement of 65.80% in Group-A and 75.07% in Group-B, p value was 0.047 showing a significant difference. (Table No. 4)

Mean Pruritus scale before the treatment in Group A was 4.06 ± 1.11 and in Group B it was 3.91 ± 1.42 . After treatment it was 2.13 ± 0.8 in Group A and 2.07 ± 0.69 , showing statistically insignificant result. (Table No. 5)

Mean sessions required to reach 50% improvement in VSS were 4.51 ± 1.3 in Group A and 3.31 ± 0.98 in group B. Results were also statistically significant with p-value 0.032. (Table No. 6)

Discussion

The treatment of keloids and hypertrophic scars is challenging and controversial. The therapeutic agents found in literature include silicone sheets, compression garments, corticosteroid injections, 5-fluorouracil (5-FU), bleomycin and interferon, topical imiquimod, cryotherapy, radiation, and laser or light-based therapies.⁶ Triamcinolone acetonide

(TCA), a corticosteroid, considered to be the first line treatment for the prevention and treatment of keloids and hypertrophic scars. In this study we evaluated the efficacy of triamcinolone acetonide alone and triamcinolone acetonide plus 5-fluorouracil for treating keloids and hypertrophic scars in burn patients, to the population that are mostly from northern Punjab, Khyber Pakhtunkhwa, Azad Jammu Kashmir and Gilgit Baltistan. The results of this study may help us to record better treatment option for keloid and hypertrophic scars for improved outcomes. Previous data in a randomized control trial by Saleem F, et al, compared the efficacy of 5-FU plus TCA versus intralesional TCA alone in the treatment of keloids and they found that 5-FU+TCA was efficacious in 98% of cases (group A) and TCA alone in 62% of cases (group B).¹⁰ In a more recent study, Khalid FA and colleagues determined the efficacy of intralesional 5-FU+TCA in comparison with TCA alone for the treatment of keloids and hypertrophic scars and they reported that the efficacy was superior in 5-FU+TCA group 77.2% than that of TCA alone group 49.09% ($p=0.002$). Recurrence was seen in 39.2% of the patients of the TCA alone group while in only 17.5% (10) of the cases of 5-FU+TCA group ($P=0.012$).¹² A recent study by Sunil Srivastava and others compared intralesional triamcinolone acetonide, 5-fluorouracil, and their combination in the treatment of keloids.¹³ There was a reduction in all parameters at every successive assessment in all three groups. Improvement in terms of height, vascularity and pliability was fastest with 5FU, TCA and TCA+5FU group, respectively, which was 75 statistically significant. Decrease in pigmentation was significantly faster with TCA+5FU. Reduction in pruritus, however, was significantly faster with 5FU than the other groups, but the difference in reduction of pain among the three groups was not significant. Telangiectasias and skin atrophy were seen most commonly in TCA group, while skin ulceration was a common problem in 5FU group. They concluded that TCA, 5FU and their combination are all effective in keloid scars. A

combination of TCA+5FU seems to offer the balanced benefit of faster and more efficacious response with lesser adverse effects when compared to individual drugs. Another meta-analysis by Ren et al concluded that TCA+5FU is safer and more efficacious than TCA alone. Studies have also shown the effectiveness of the combination therapy to be significantly better than 5FU.¹⁴ Another study compared the use of intralesional TAC alone and its combination with 5-FU for the treatment of keloid and hypertrophic scars.¹⁵ The combination used, 45 mg of 5-FU (0.9 mL of 250 mg/5 mL) and 4 mg of TCA (0.1 mL of 40 mg/1 mL), was administered weekly for 8 weeks. This combination had already been reported as effective.¹⁶ The study found that the combination therapy was superior to TCA alone in reducing the initial height of the scar, also offering a faster response, with 76 fewer undesirable effects, such as skin atrophy and telangiectasias. Similar findings were reported in other studies.^{17, 18} We experienced some complications in few of the patients who were treated with 5FU, which included necrosis, blister formation, hyperpigmentation and ulceration of the skin. These complications were managed accordingly. Management involved stopping 5FU injections, daily dressing, excision of the necrosed tissue and primary closure. We hypothesized that the injection technique was the cause of those complications injecting 5FU in superficial plane until the blanching of the scar occurs. Later we changed the technique and injected 5FU in deeper planes and avoided blanching of the skin of the scar. After changing technique, rate of complications fell drastically. This study has some limitation like major portion of our population consisted of female gender and complications of both treatments were not compared.

Conclusion

Combination therapy of intra-lesion injection of triamcinolone acetonide and 5-fluorouracil has significantly higher efficacy as compared to

triamcinolone acetonide alone for the treatment of keloids and hypertrophic scars. For resistant or recurrent scars, combination therapy can be used as 1st line treatment but precautions have to be taken keeping in view the complications of blisters and necrosis, if injected superficially.

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