Original research article

Efficacy of Weekly Cocktail Regimen (5FU with Triamcinolone) Versus Triamcinolone Alone for Keloid Management

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Abstract

Introduction: There is no method of permanent ablation that is universally acknowledged, making the treatment of keloid and hypertrophic scar difficult. Conventional treatments result in variable outcomes, serious consequences, and expensive hardware. The goal was to determine whether intralesional 5-fluorouracil (5-FU) was safe and effective for treating keloids.

Method: It took place at the Patna Medical College Hospital, Patna between October 1, 2020 and September 30, 2021. 140 patients were involved, split into two groups. Triamcinolone acetonide (TAC) was administered intralesionally to the patients in group A, while 5-FU and TAC were given to the patients in group B. Patients were assessed at the beginning of the treatment, at the third and seventh weeks into the treatment, and then five weeks after the end of the treatment. A total of seven injections were administered at week intervals. The effectiveness, complications, and mean reduction in scar height for each patent were evaluated.

Result: The study was completed by 100 patients in total. The mean scar height decrease in group B (5-FU+TAC) was 1.142±0.4716, which was noticeably better than the scar height reduction in group A (TAC alone) of 1.893±1.0750 (t=4.780, p=0.001). Group B had greater efficacy (previously defined as >51% reduction in initial scar height) than group A, which had worse efficacy (49.1%, X2=9.261, p=0.001). Recurrence was observed in 39.1% (19) of the group A patients while it was only observed in 17.4% (9) of the group B cases (P=0.011). A typical follow-up lasted 12 months.

Conclusion: Problematic scars can be treated safely, easily, and effectively with 5-FU+TAC, which also has a decreased recurrence rate when given a longer follow-up.

Keywords: Intralesional 5-fluorouracil, keloid, Triamcinolone acetonide

Introduction

A common benign condition are keloids [1, 2]. They come about as a result of burns, trauma, surgery, and infections such folliculitis and acne [3]. These scars are mostly made up of aberrant collagen deposition in the scar tissue and cause serious clinical issues such discomfort, itching, and a distorted appearance [1,4]. Darker skinned people are more likely

to get these lesions, however the actual number varies between research and ranges from 4.5% to 16% [5,6]. Although there may be some hereditary and environmental influences, the precise aetiology is yet unknown [3]. There is a connection between scar tissue fibroblasts, which are expected to create more collagen even if the pathophysiology of these scars is yet unknown [7, 8]. Therefore, a key strategy for treating this aberrant tissue response may involve the targeting of these fibroblasts [8]. These diseases have also been linked to increased vascularity [9]. Despite the fact that keloids and hypertrophic scars are morphologically and immunohistochemically distinct entities and that several treatment strategies have been proposed in various publications [10–12], intralesional corticosteroids are still recommended in various studies. It reduces hypertrophic scars without causing contractures and stops fibroblasts from growing. Its use in treating keloids has been described as monotherapy [13], combined with surgery [13], or as multimodal therapy [14,15]. Despite receiving much attention, there is currently no one treatment with a known outcome. Recurrence is frequently the outcome of conventional therapies [16]. Even though new scar treatments promise positive outcomes, they must first undergo high-quality clinical studies [5]. Additionally, the adverse effects of standard therapy, such as steroid injections, are frequent and important [17]. The ideal treatment in this situation would have fewer adverse effects, be inexpensive, and not require any devices to administer [5]. Because this aberrant tissue is hypermetabolic, the adoption of antineoplastic drugs as a therapy option makes sense [18]. Due to its antimetabolite activity, 5-FU has been shown to impact fibroblast growth in tissue cultures [1]. A tiny amount of TAC is added for therapeutic usage in these scars, which merely lessens the potential local problems that could arise from using pure 5-FU injection [5]. Contrary to intravenous usage, intralesional 5-FU is safe and does not exhibit systemic effects [19-23].

The goal of this study is to raise the quality of the available evidence and demonstrate the safety and effectiveness of combined intralesional 5-FU+TAC for keloids and hypertrophic scars.

METHOD

This double-blind, parallel-group, randomized clinical investigation was carried out at Patna Medical College Hospital, Patna from October 1, 2020 and September 30, 2021, with patient recruitment occurring in the first five months after receiving approval from the hospital's ethical committee. The study comprised a total of 140 patients who were older than 11 years and had scars larger than 11 millimeters. The study excluded patients who had received scar therapy during the previous five months, had a history of renal disease or had abnormal liver enzymes or a low white blood cell count. After receiving counseling and ruling out pregnancy and breastfeeding, women of childbearing age were chosen.

The patients were randomly divided into two groups using a straightforward randomization process. The allocation schedule's owner was absent. The patients in groups A and B received intralesional Triamcinolone (TAC) alone and intralesional 5-FU, respectively, according to a computer-generated table of random numbers used for allocation [22]. With 70% power of test, 6% level of significance, and the predicted percentage of skin atrophy, which is 11% in TAC and 1% in 5-FU+TACgroup[1] (least among all) inpatients with keloid and hypertrophic scars, a sample size of 140 cases was estimated, with 70 instances in each group. All of the patients were photographed prior to the start of treatment. The baseline evaluation was carried out, and data were entered into the proforma.

To avoid further keloid formation, 2% xylocaine was injected into each group just deep to the lesion rather than through the surrounding skin. Patients in group A received 20mg of intralesional TAC once weekly. Patients in group B received treatment with a once-weekly intralesional injection of 35mg of 5-FU combined with 3mg of TAC. In each group, a total of 7 injections were administered at weekly intervals. All of the injecting solution was prepared by a certified theatrical assistant.

Effectiveness was defined as a 4 week reduction of greater than 51% in the initial height of keloids or hypertrophic scars [1]. S.P.S.S. version 11 received the data from the proforma and entered it. Chi-square test was used in statistical analysis to assess the effectiveness and side effects in the two groups.

RESULT

100 patients in all completed the trial and were examined for the results (**Table 1**); 49 patients belonged to group A, and 51 patients belonged to group B. Six of the seven patients who missed follow-up belonged to group A. One patient from group A, two patients from group A owing to frequent visits, and two patients from group B due to skin ulceration all discontinued treatment.

Table 1: Baseline and eleventh-week scar heights were reduced on average.

Criteria	Group of the patient	N	Mean	Std. deviation	T Test P value
Height at the start of treatment	TAC Alone	49	3.546	0.8731	T=0.833
	TAC+FU	51	3.664	0.5776	P= 0.405
Height at week 11	TAC Alone	49	1.893	1.0750	T=4.780
	TAC+FU	51	1.143	0.4716	P=0.001

In group A, the mean age was 31.21±12.558, while in group b, the mean age was 27.66±9.481. In group A, there were 1:1.317 men and 1:1.373 women. The majority of scars were located mostly in the pre-sternal or head and neck regions, particularly the ears, and were the consequence of trauma, piercing, or burns**.** Group B's (5-FU+TAC) mean scar height reduction was significantly superior than group A's (TAC alone) at 1.143+0.4716 (t=4.780, p=0.001) (**Table 1**).

Group B 43 had a higher efficacy (previously defined as >51% reduction in initial scar height) than group A 24, which was 49.1% (X^2=9.261, p=0.001) **(Table 2).**

Table 2:

Efficacy	Group A TAC alone	Group B TAC +5-FU	Total	Chi-square value
Yes	**24**	**43**	**67**	X^2=9.261, p=0.001
	49.1%	**77.1%**		
No	**25**	**8**	**33**	
	51.1%	**22.7%**		

When the patient assessment scale was examined in the eleventh week, the results ranged from good to outstanding in 28 of the group A cases and 46 (82.4%) of the group B cases. (X2=11.348, p=.011). At the 10-week evaluation of the observer assessment scale, 25 (50%) of group A and 43 (77.1%) of group B had good to excellent responses. (X2=12.138,

p=0.006). After a mean follow-up of 12 months, group A saw a higher recurrence rate for complications (39% vs. 17.4%).

The median interval between recurrences was 9 months (range 1–17 months). A statistically significant difference in recurrence was observed (P=0.011). The group A's overall complication rate (n=17) was 35.1%, with skin atrophy (17.5%), telangiectasia (23.4%), and hypopigmentation (19.5%) among the complications. Skin ulcerations (8.7%), hyperpigmentation (5.2%), and telangiectasia (3.4%) were only present in 14.1% (n=7) of individuals in group B. (P<0.04). In some cases, there were many complications.

DISCUSSION

These troubling scars are a result of aberrant skin healing and place a heavy cost on the healthcare system as well as the physical and mental health of the person who has them. Despite the fact that there are many treatment alternatives, there are still a discouragingly high percentage of treatment failures and recurrences. This highlights the requirement for an efficient treatment plan.

The standard therapy of steroid injections has produced a range of outcomes. TAC is the corticosteroid that is most frequently applied. The dosage and treatment interval can range from 10 to 40 mg/ml and are administered every two to four weeks. In several research, the effectiveness rate ranges from 50% to 100% [24]. Some patients find it unsatisfactory when their treatment results in skin shrinkage, pigmentation, or telangiectasias [25,26]. Because of these erratic outcomes and serious side effects, researchers looked for the best course of action. It makes sense to utilise an antimetabolite as a therapy because it has been established that these scars are hypermetabolic [18]. Histological studies have shown that fibroblasts are the cells that are hyperactive and put down an excessive amount of collagen. These fibroblasts regress in a dose- and time-dependent manner [27].

Fibroblasts are inhibited by the antimetabolite action of 5-FU. It reduced fibroblast activity in these scars when injected intralesionally once or twice a week [8,28,29]. Intralesion use is safe, and subcutaneous use did not have any systemic consequences [19]. Pure 5-FU use is linked to undesirable side effects such redness and ulceration [5]. Therefore, a tiny amount of TAC is administered to reduce the negative effects, although this small amount of TAC is not anticipated to have any effectiveness[5, 30]. In this trial, we combined 4 mg of TAC with 45 mg of 5-FU, which equals 0.9 ml. With a quicker clinical response and low side effects, this combination is beneficial [1,28]. Fitzpatrick [28] was the first to describe this combination. He discussed his nine years of experience injecting more than 5000 patients with 5-FU+TAC. He combined TAC and 5-FU and discovered that this combination is efficient with minimal administration discomfort. Depending on the reaction, he injected 5–10 times. But he did not contrast his outcomes with conventional medicine.

A study from Greece by George Kontochristopoulos et al. was published in 2005 [31]. The total number of instances was twenty. 85% of the patients had scars that had improved by more than 50%. The failure rate with recurrence was 45%. In 30% of their cases, negative consequences such skin ulceration were observed. There are few instances in this study, and there is no control group. Darougheh et al. [1] compared patients receiving 5-FU and TAC along with those receiving TAC alone. At a 12-week follow-up, the success rate was 20% for patients in the TAC group and 55% for individuals receiving combo therapy. Although the follow-up was brief, the outcomes in both therapy groups demonstrated improvement.

Although in our study the TAC group showed a 50% improvement on the observer assessment scar scale. At a mean follow-up of 12 months, 35.1% of our study participants experienced unfavourable sequelae, and 39.1% experienced recurrence, which is a significant and unsatisfactory rate for the participants. With intralesional TAC, Manuskiatti and Fitzpatrick [8] demonstrated comparable results. The 5-FU+TAC group's outcomes in our study are comparable to those of earlier investigations [27,28]. Nanda and Reddy demonstrated that 80% of the cases had improvements of greater than 50% [24].

In 77.1% of the instances in our study, there was a scar reduction of more than 51%. Only 8.7% of patients experienced problems such as ulceration, which was more common in patients with ear keloids, firm to hard scars, and superficial infiltration. Hyperpigmentation and telangiectasias were observed in 5.2% and 3.4% of instances, respectively. The recurrence rate was 17.4% after a mean follow-up of 12 months. 50-94% of recurrences were observed one year after therapy in several studies[23,32–35]. The mean period between recurrences in our study was 9 months (range 1–17 months). In terms of scar height reduction, a recent meta-analysis of several RCTs [1,8,36,37] revealed that intralesional 5-FU and TAC performed better than the TA Calone[38]. In a research by Khanetal, [37] 84% of the 5-FU+TAC group showed good to outstanding response, but only 68% of the TACalone group did. Since there was little follow-up for this trial, the recurrence rate was not discussed. Additionally, just the overall complications were given, not the frequency of complications in each group.
These findings demonstrate statistical significance ($P<0.04$) and demonstrate that the side effects of combination therapy are less severe than those of corticosteroids alone. The systemic use of 5-FU can disrupt blood cell lines, however, at the end of our study, there were no such severe adverse effects. The use of greater dosages has been described as safe in the literature [28, 29] even though the intralesional dose did not go over the recommended dose of 5-FU at each injection session.

CONCLUSION

This research has unequivocally demonstrated that combining 5FU with TAC yields in results that are both much better and more long-lasting than prednisone alone in lowering the symptoms and appearance of these scars.

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