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Efficacy of Combined Intralesional Triamcilone and Cryotherapy for Treatment of Keloid

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ABSTRACT

Keloid treatment remains a challenging task due to the high recurrence rates and limited effectiveness of monotherapies. **Objective:** To determine the efficacy of combining intralesional Triamcinolone Acetonide (TA) with cryotherapy. **Methods:** A quasi-experimental study was conducted at the Dermatology Department, Nishtar Hospital, Multan, over 6 months from 30th June 2024, to December 31, 2024. Eighty patients were enrolled using non-probability consecutive sampling. Baseline characteristics, including keloid dimensions, pain, and itching scores, were documented. Patients received cryotherapy followed by intralesional TA (40 mg/mL) injections for up to six sessions. Treatment outcomes were assessed two weeks post-treatment through reduction in keloid height, length, and Visual Analog Scale (VAS) scores. **Results:** The mean keloid height and length reduced significantly from 4.66 ± 1.37 mm to 1.69 ± 1.18 mm and 6.64 ± 2.23 cm to 2.68 ± 1.79 cm, respectively ($p < 0.001$) post-treatment. VAS pain scores decreased by 2.86 ± 1.96, and VAS itching scores decreased by 3.53 ± 1.39 ($p < 0.001$). Efficacy, defined as ≥50% reduction in keloid dimensions, was achieved in 75% of participants. Common adverse effects included blistering (18.8%) and erythema (15%). **Conclusions:** The combination of cryotherapy and intralesional triamcinolone acetonide demonstrated effective reduction in keloid height and length, with significant improvement in pain and itching scores. Although efficacy varied across demographic and lesion-specific variables, the treatment remains a safe and viable option for keloid management, with manageable adverse effects and promising outcomes.

INTRODUCTION

Keloids are caused by aberrant wound-healing process, due to excessive fibroblast proliferation, persistent inflammation, and dysregulated Extracellular Matrix (ECM) deposition beyond the original wound. They do not regress spontaneously, and often recur after removal [1]. Keloid are frequently observed in the African and Asian population. The prevalence of keloids can varies across different geographical regions, as 0.09% in United Kingdom to as high as 16% in Africa [2]. In addition to cosmetic defect, it can cause substantial discomfort, including itching, pain, and restricted movement. In severe cases, keloids may ulcerate and, rarely, undergo neoplastic progression, making treatment necessary not just for cosmetic reasons but also for medical reasons [2, 3]. Molecular signaling pathways like TGF-β/Smad and JAK/STAT play a key role in keloid progression by activating fibroblast activation, collagen production, and immune responses. TGF-β1, a major cytokine, boosts fibroblast growth, increases Extracellular Matrix (ECM) buildup, and prevents cell death, leading to persistent structural changes. Chronic inflammation from prolonged pro-inflammatory signals worsens fibroblast activity. Mechanical stress and low oxygen levels further aggravate this process. Effective treatments must target fibroblast growth, inflammation, and ECM to prevent proliferation and fibrotic changes [4, 5]. Various therapeutic interventions have been explored,

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including non-invasive methods like silicone gel and pressure therapy to invasive options like intralesional corticosteroids, 5-fluorouracil, cryotherapy, laser therapy, and surgical excision [6]. Intralesional corticosteroids, particularly triamcinolone acetonide, remain a primary treatment for keloid due to their ability to inhibit collagen synthesis, reduce fibroblast proliferation, and relieve symptoms like itching and pain [7, 8]. Cryotherapy treats keloids by applying extremely cold liquid nitrogen, to induce fibroblast apoptosis and reduce collagen synthesis by altering fibroblast phenotype, increasing the type III to type I collagen ratio. Furthermore, through scar tissue softening, it improves corticosteroid penetration. However, the efficacy of cryotherapy as a monotherapy remains questionable, with some studies suggesting a favorable response, whereas others indicate limited benefit [2, 9]. A combination of cryotherapy and intralesional corticosteroids may exert a synergistic effect, achieving better therapeutic outcomes compared to either treatment alone [10]. Despite ongoing progress in skin treatments, managing keloids remains difficult due to their tendency to return and poor response to standard therapies. This study was designed to assess how well a combination of intralesional corticosteroid injections and cryotherapy works for treating keloids. It focused on changes in the size of the lesions, along with improvements in pain and itching.

The goal was to explore whether this combined approach offers better outcomes.

METHODS

This quasi-experimental study was conducted at the Dermatology Department, Nishtar Hospital, Multan, after obtaining approval from the Institutional Review Board (IRB No. 7110), over six months from June 2024 to December 2024. A total of 80 patients were enrolled using non-probability consecutive sampling, with the sample size calculated using the WHO sample size calculator, assuming a 95% confidence level and an anticipated efficacy rate of 71.1%, based on previous studies. The study included adults aged 18 to 60 years with non-flattened keloids (up to 10 cm) present for over six months on various body sites. Preference was given to those with symptoms such as pain, itching, or cosmetic concerns, who agreed to treatment, follow-up, and photography. Patients with conditions such as pregnancy, breastfeeding, allergies to treatment, hypertrophic scars, infections, serious health issues, or recent use of corticosteroids, anticoagulants, or immunosuppressants were excluded. Baseline assessment included a clinical examination by a consultant dermatologist to confirm keloid diagnosis, with documentation of age, gender, keloid duration, site, cause (e.g., trauma, burn, surgery), lesion size, and symptom severity. Pain and itching were assessed using the Visual Analog Scale (VAS), which ranges from 1 (no pain/itching) to 10 (severe pain/itching). Treatment protocol involved the application of Eutectic Mixture of Local Anesthetics (EMLA) cream one hour before cryotherapy to reduce discomfort. Cryotherapy was performed by spraying liquid nitrogen onto the lesion, followed by two freeze-thaw cycles, with intralesional triamcinolone acetonide (40 mg/mL) injection five minutes after cryotherapy. Cryotherapy was repeated weekly for up to six sessions, with patients advised to keep the treated area clean and dry. Adverse effects, including blistering, erythema, ulceration, and skin discoloration, were documented during follow-up visits. The outcome assessment was based on keloid height and length, and efficacy was defined as a ≥50% reduction in keloid dimensions from baseline. Safety assessment involved documenting any adverse effects, and statistical analysis was performed using SPSS version 26.0, with paired t-tests for pre- and post-treatment comparisons. A p-value of ≤ 0.05 was considered statistically significant [11-13].

RESULTS

The study included 80 participants, with a majority being female 58 (72.5%), while males comprised 22 (27.5%). The mean age of participants was 35.98 ± 11.22 years. Most individuals were aged 18–39 years 50 (62.5%), while 30 (37.5%) were in the 40–60 years group. Etiologies included surgical wounds in 24 (30%), acne in 21 (26.3%), burns in 13 (16.3%), trauma in 9 (11.3%), and unknown causes in 13 (16.3%). Lesions were most commonly distributed on the abdomen 25 (31.3%), followed by the pubic area and extremities (18 each, 22.5%), armpits (7, 8.8%), and the chest and back (6 each, 7.5%). The mean duration of keloids was 2.50 ± 1.13 years. The mean percentage decrease in height was 68.21 ± 20.58%, while the mean percentage decrease in length was 63.69 ± 18.89%. The average keloid height reduced from 4.66 mm to 1.69 mm, and length from 6.64 cm to 2.68 cm, both showing statistically significant improvement ($p < 0.001$). VAS pain scores dropped from 5.35 to 2.49, and itching scores from 6.46 to 2.94, indicating marked symptom relief following treatment ($p < 0.001$ for both measures) (Table 1).

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Table 1: Comparison of Study Variable Befor and After Treatment

Variable	Pre-Treatment Mean ± SD	Post-Treatment Mean ± SD	Mean Difference Mean ± SD	95% CI (Lower- Upper)	p-Value
Height of keloid (mm)	4.66 ± 1.37	1.69 ± 1.18	2.98 ± 0.65	2.83-3.12	<0.001
Length of keloid (cm)	6.64 ± 2.23	2.68 ± 1.79	3.96 ± 1.07	3.72-4.20	<0.001
VAS pain	5.35 ± 1.61	2.49 ± 1.09	2.86 ± 1.96	2.43-3.30	<0.001
VAS itching	6.46 ± 1.12	2.94 ± 0.77	3.53 ± 1.39	3.21-3.84	<0.001

Improvement in keloid length was observed in 41 participants (51.3%) with a 50-74% reduction, 20 (25%) with a 0-49% reduction, 8 (10%) with a 75-90% reduction, and 11 (13.8%) with more than 90% reduction. Improvement in keloid height was noted in 40 participants (50%) with a 50-74% reduction, 10 (12.5%) with a 0-49% reduction, 12 (15%) with a 75-90% reduction, and 18 (22.5%) with more than 90% reduction.

Efficacy (≥ 50% reduction of keloid height and length from baseline)

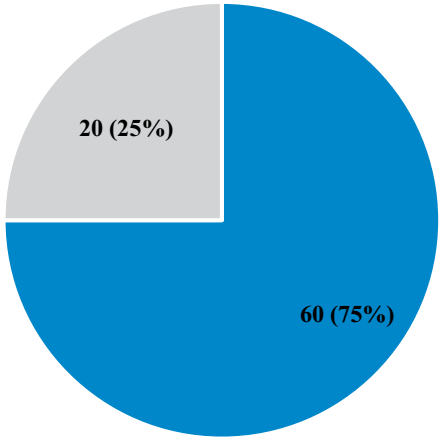

Figure 1: Distribution of Treatment Efficacy (n=80)

The treatment was associated with various adverse effects, as shown in the table 2.

Table 2: Adverse Effects Observed During Treatment

Adverse Effect	Frequency (%)
Blistering	15 (18.8%)
Ulceration	3 (3.8%)
Erythema	12 (15%)
Skin discoloration (hypo-/hyperpigmentation)	6 (7.5%)
Overall adverse effects	20 (25%)

Efficacy was higher in females (79.3%) compared to males (63.6%) with no significant gender association (p = 0.148). Younger participants (18-39 years) showed slightly better efficacy (76.0%) than those aged 40-60 years (73.3%), but the difference was not statistically significant (p = 0.790). Lesion location also showed no significant association with efficacy (p = 0.400), although efficacy was highest for armpit lesions (100%) and lowest for abdomen lesions (64.0%).

Table 3: Stratification of Baseline Variables and Their Association with Treatment Efficacy

Variables	Efficacy		p-Value
	Yes Frequency (%)	No Frequency (%)	
Gender			
Male	14 (63.6%)	8 (36.4%)	0.148
Female	46 (79.3%)	12 (20.7%)	
Age Group			
18-39 Years	38 (76.0%)	12 (24.0%)	0.790
40-60 Years	22 (73.3%)	8 (26.7%)	
Keloid Location			
Chest	4 (66.7%)	2 (33.3%)	0.400
Back	5 (83.3%)	1 (16.7%)	
Abdomen	16 (64.0%)	9 (36.0%)	
Pubic	15 (83.3%)	3 (16.7%)	
Armpit	7 (100.0%)	0 (0.0%)	
Extremities	13 (72.2%)	5 (27.8%)	

DISCUSSION

Managing keloids remains clinically challenging due to their frequent recurrence and inconsistent response to treatment [14].Fibroblast overactivity, collagen buildup, and ongoing inflammation contribute to this complexity. Intralesional corticosteroids like triamcinolone acetonide are commonly used for their anti-inflammatory effects, while cryotherapy helps by damaging abnormal tissue and enhancing drug absorption [2, 15]. Studies have shown that combination therapies are often more effective than single treatments, offering better results by addressing several underlying mechanisms at once [10, 16].In the present study, efficacy was defined as achieving ≥50% reduction in both keloid height and length. Based on this criterion, 75% of patients showed effective improvement.These findings are supported by prior literature.Mutalik S, reported an 87.7% overall improvement with combination therapy, including 1.3% with >90% improvement,46.4% with 75–90%, and 41.2% with 50–74% reduction [17]. Jwa SJ *et al.*, observed a 90.7% non-recurrence rate in 54 patients treated with cryotherapy plus triamcinolone acetonide (TA) after excision [18]. Cohen AJ *et al.*, also demonstrated that 71.1% of patients achieved >50% reduction with combination therapy, versus 43% with TA alone (p = 0.0021) [10].The efficacy of cryotherapy-enhanced intralesional corticosteroid therapy was also supported by Ahsan MQ *et al.*, who observed a 90% improvement rate in their combination therapy group, compared to 83.3% in the TA monotherapy group [16].Similarly, Jannati P *et al.*, compared cryotherapy combined with either TA or verapamil, reporting that 70% of patients receiving TA plus

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cryotherapy achieved complete resolution, while 65% of those treated with verapamil plus cryotherapy showed similar results, suggesting that the addition of cryotherapy significantly enhances therapeutic outcomes [19].The improvement rates observed in this study, where 50% of participants had a 50-74% reduction in keloid height and 22.5% experienced >90% improvement, align closely, found that 46.4% of patients achieved 75-90% improvement, and 11.1% had >90% improvement. Further supporting these findings, Singh PK *et al.*, reported a significantly higher response rate in patients receiving TA and cryotherapy compared to TA alone, with 48% of lesions flattening in the combination group versus only 16% in the monotherapy group [20]. Hewedy ES *et al.*, in a systematic review, highlighted the synergistic effect of cryotherapy, demonstrating that it enhances corticosteroid penetration, promotes fibroblast apoptosis, and reduces local inflammation, complementing TA's anti-inflammatory properties [21].In this study, the mean reduction in VAS pain score was 2.86 ± 1.96 ($p < 0.001$), while the mean decrease in VAS itching score was 3.53 ± 1.39 ($p < 0.001$). This aligns with findings from prior studies demonstrating significant symptomatic relief following combination therapy.A study comparing TA monotherapy to TA combined with cryotherapy reported a notable decrease in pain and itching scores post-treatment, with pain reducing from 5.8 ± 2.1 to 3.2 ± 1.6 ($p = 0.000$) and itching decreasing from 5.8 ± 2.2 to 3.9 ± 2.0 ($p = 0.001$) in the combination therapy group [17]. Cohen AJ *et al.*, study also highlighted that pruritus and pain were significantly reduced [10]. These findings further reinforce these results, where a substantial reduction in both VAS pain and itching scores ($p < 0.001$) was observed.Furthermore, Yosipovitch *et al.*, demonstrated that triamcinolone alone or in combination with cryotherapy resulted in marked pain and pruritus relief, supporting these findings [11].Despite the observed improvements, variations in pain and itching reduction across studies may be attributed to differences in lesion characteristics, treatment protocols, and patient sensitivity to procedural pain [13, 18, 21].The adverse effects observed in this study were consistent with findings from previous literature evaluating the combination of cryotherapy and intralesional Triamcinolone Acetonide (TA) for keloid treatment.In this study, the most common adverse effects included blistering (18.8%), ulceration (3.8%), erythema (15.0%), and skin discoloration (7.5%), with an overall incidence of 25%. Another study comparing TA alone versus TA with cryotherapy found telangiectasia in 29.9% and hyperpigmentation in 11.6% of the control group, whereas blistering (68.6%) and hypopigmentation (25.5%) were significantly higher in the combined therapy group [17]. Similarly, Ahsan MQ *et al.*, observed ulceration in 12.5%, hypopigmentation in 50%, and hyperpigmentation in 34.4% of patients undergoing combination therapy [16]. Yosipovitch *et al.*, reported that hyperpigmentation occurred in only one patient [11].A systematic review by Hewedy ES *et al.*, further corroborated these findings, highlighting that combination therapy increases the likelihood of temporary blistering and pigmentary changes but does not lead to severe or persistent complications [21].The differences in reported adverse event rates across studies may be attributed to variations in treatment protocols and patient skin types.While cryotherapy enhances corticosteroid penetration and keloid regression, it is associated with a higher incidence of transient side effects such as blistering and pigmentary alterations.Previous studies have also assessed how gender, age, and lesion site influence keloid treatment response. Jannati P *et al.*, found higher response rates in females, though not statistically significant.This is similar to these findings, where females showed 79.3 percent efficacy compared to 63.6 percent in males ($p = 0.148$)[19]. Similarly, Singh PK *et al.*, reported better outcomes in younger individuals, which aligns with this data: participants aged 18 to 39 years showed 76 percent efficacy, while those aged 40 to 60 years had 73.3 percent ($p = 0.790$)[20]. Regarding lesion location, Hewedy ES *et al.*, observed better results on the chest and limbs, this study showed highest efficacy in armpit lesions (100 percent) and lowest on the abdomen (64.0 percent) ($p = 0.400$) [21]. Ahsan MQ *et al.*, Additionally, chest keloids demonstrated the highest response (34.6%), whereas back lesions had the lowest (5.8%), a trend consistent with this study findings [16].These findings suggest that although demographic and anatomical variations influence treatment response, they do not significantly alter overall efficacy, reaffirming the consistency of these results with prior research.Limitations of study includes the short follow-up duration which restricts the ability to provide information related to long-term recurrence rates. Future research should focus on larger, multi-center trials with longer follow-up to better evaluate recurrence and refine treatment procedures.Despite these limitations, the findings of this study strengthen the growing evidence that combination therapy offers superior efficacy compared to monotherapy, supporting its continued use in clinical practice.

CONCLUSIONS

This study demonstrates the efficacy of combining cryotherapy with intralesional triamcinolone acetonide for keloid treatment, attaining significant reductions in keloid size along with improvements in symptoms such as pain and itching. The results confirm the therapeutic potential of this multimodal approach, offering a safe option for the

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management of keloids. Demographic factors, such as gender, age, and lesion location didn't report significant associations with treatment efficacy, confirming the broader applicability of combined therapy.

Authors Contribution

Conceptualization: ST
Methodology: ST, RT, N
Formal analysis: MIJ
Writing, review and editing: RT, N, MTS, MS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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