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*Original Research Article*

# Efficacy of Topical 0.1% Tacrolimus versus Topical 0.05% Clobetasol Propionate for the Treatment of Vitiligo in Terms of Repigmentation

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***Abstract***: ***Objective:*** Vitiligo is an acquired depigmenting disorder with profound psychosocial impact. The present randomized controlled trial compared the efficacy and safety of topical 0.1% tacrolimus and 0.05% clobetasol propionate for inducing repigmentation in patients with stable vitiligo. ***Methods***: A randomized controlled study was conducted in the Department of Dermatology, Shaikh Zayed Hospital, Lahore, from March to September 2025. Sixty patients aged 15–40 years with stable non-segmental vitiligo involving <25% body-surface area were randomly assigned to receive either topical tacrolimus 0.1% ointment (Group A) or clobetasol propionate 0.05% ointment (Group B) once daily for 24 weeks. Repigmentation was graded (G0–G4) based on standardized photographs; successful repigmentation was defined as ≥50% improvement. Data were analyzed using SPSS v26 with $p < 0.05$ significant. Results: Mean age was 28.7 ± 6.1 years (43.3% male, 56.7% female). At 24 weeks, successful repigmentation was achieved in 21 (70%) tacrolimus patients and 16 (53.3%) clobetasol patients ($p = 0.041$). Mean repigmentation score was 2.96 ± 0.71 vs 2.41 ± 0.66 ($p = 0.018$). Transient burning and erythema occurred in 10% of tacrolimus users; skin atrophy and acneiform eruption in 13.3% of clobetasol users. No systemic adverse effects were reported. ***Conclusion:*** Topical 0.1% tacrolimus was significantly more effective and safer than 0.05% clobetasol propionate for repigmentation in stable vitiligo. Tacrolimus is recommended as a first-line therapy, especially for facial and intertriginous lesions.

*Keywords*: Vitiligo, Tacrolimus, Clobetasol propionate, Calcineurin inhibitor, Topical therapy, Repigmentation.

## INTRODUCTION

Vitiligo is an acquired idiopathic pigmentary disorder characterized by well-demarcated white macules and patches due to loss or dysfunction of melanocytes. Globally, its prevalence ranges from 0.5 to 2%, with significant psychological burden and social stigma, particularly in dark-skinned populations[1]. The condition follows a chronic course with periods of stability and progression. Although not life-threatening, its cosmetic impact can be devastating,

leading to depression, anxiety, and social withdrawal[2]. Pakistan reports a relatively high frequency of vitiligo, yet standardized treatment guidelines are lacking.

Multiple theories attempt to explain its pathogenesis. The autoimmune theory is the most widely accepted, proposing that cytotoxic T-cells and melanocyte-specific autoantibodies induce cell destruction[3]. This is supported by the association of vitiligo with other autoimmune diseases such as thyroiditis, type 1 diabetes, and pernicious anemia[4]. The auto-cytotoxicity theory postulates that melanocytes undergo oxidative injury due to accumulation of toxic melanin precursors and reactive oxygen species[5]. Genetic predisposition, neurogenic factors, and environmental stressors also play important roles[6].

Topical corticosteroids remain the mainstay of medical treatment because of their potent anti-inflammatory and immunosuppressive properties[7]. However, chronic use of potent agents like clobetasol propionate may lead to skin atrophy, telangiectasia, striae, perioral dermatitis, and tachyphylaxis[8]. Hence, alternative treatments that offer similar efficacy without steroid-related toxicity are highly desirable.

Calcineurin inhibitors such as tacrolimus and pimecrolimus represent one of the most promising non-steroidal options. Tacrolimus is a macrolide lactone that inhibits calcineurin-mediated activation of T-lymphocytes by preventing dephosphorylation of NFAT, thereby suppressing interleukin-2 and other cytokines[9]. Unlike steroids, tacrolimus does not interfere with collagen metabolism and thus avoids dermal atrophy[10]. Furthermore, in vitro studies suggest that tacrolimus stimulates melanogenesis and melanocyte migration[11].

Several clinical studies have confirmed its efficacy. Lee and Kwon found that calcineurin inhibitors produced excellent repigmentation on the face and neck compared to other sites[12]. Mumtaz et al. reported a 70% success rate for tacrolimus versus 47.6% for clobetasol in a Pakistani cohort[13]. However, data from local tertiary centers remain scarce. This study therefore aimed to compare the efficacy and safety of topical 0.1% tacrolimus with 0.05% clobetasol propionate for stable vitiligo in a Pakistani population.

## Patients and Methods

This randomized controlled trial was conducted at the Department of Dermatology, Shaikh Zayed Hospital, Lahore, after ethical approval (reference DER/2024/03). The study complied with the Declaration of Helsinki. Patients aged 15–40 years with clinically stable vitiligo (no new lesions for ≥3 months confirmed under Wood's lamp) and <25% body-surface involvement were included. Exclusion criteria comprised lip-tip vitiligo, pregnancy or lactation, recent treatment within four weeks, autoimmune or psychiatric disorders, hypersensitivity to study drugs, and current or past malignancy.

After written informed consent, patients were randomly allocated (30 per arm) by lottery method to receive either topical tacrolimus 0.1% (Group A) or clobetasol propionate 0.05% (Group B). Both were applied once daily at bedtime as a thin film over depigmented areas. Sunscreen use and avoidance of trauma were emphasized. No other topical or systemic therapy was allowed.

Baseline data included age, sex, disease duration, lesion site, and area. Standardized photographs were taken at baseline, 12, and 24 weeks under consistent illumination. Three blinded dermatologists independently graded repigmentation using a five-point scale: G0 (no repigmentation), G1 (<25%), G2 (25–49%), G3 (50–75%), G4 (>75%). Responses ≥ G3 were deemed successful. Adverse events such as erythema, pruritus, burning, folliculitis, and atrophy were recorded.

Statistical analysis was performed using SPSS v26. Quantitative variables were expressed as mean ± SD and compared using t-tests. Categorical variables were analyzed using Chi-square tests. Significance was set at $p < 0.05$.

# RESULTS

Sixty patients completed the study without loss to follow-up. The mean age was 28.7 ± 6.1 years (16–39 years). There were 26 males (43.3%) and 34 females (56.7%). Average disease duration was 19 ± 7 months and mean lesion size 4.8 ± 2.4 cm². Baseline characteristics were comparable between groups ($p > 0.05$).

**Table 1: Baseline Characteristics**

| Variable | Tacrolimus (n=30) | Clobetasol (n=30) | p-value |
|---|---|---|---|
| Mean age (years) | 28.4 | 29.1 | 0.61 |
| Gender (M/F) | 12/18 | 14/16 | 0.59 |
| Mean disease duration (months) | 19.3 | 18.7 | 0.78 |
| Mean lesion size (cm²) | 4.7 | 4.9 | 0.82 |
| Face involvement (%) | 36.7 | 33.3 | 0.78 |
| Extremity involvement (%) | 50.0 | 53.3 | 0.79 |

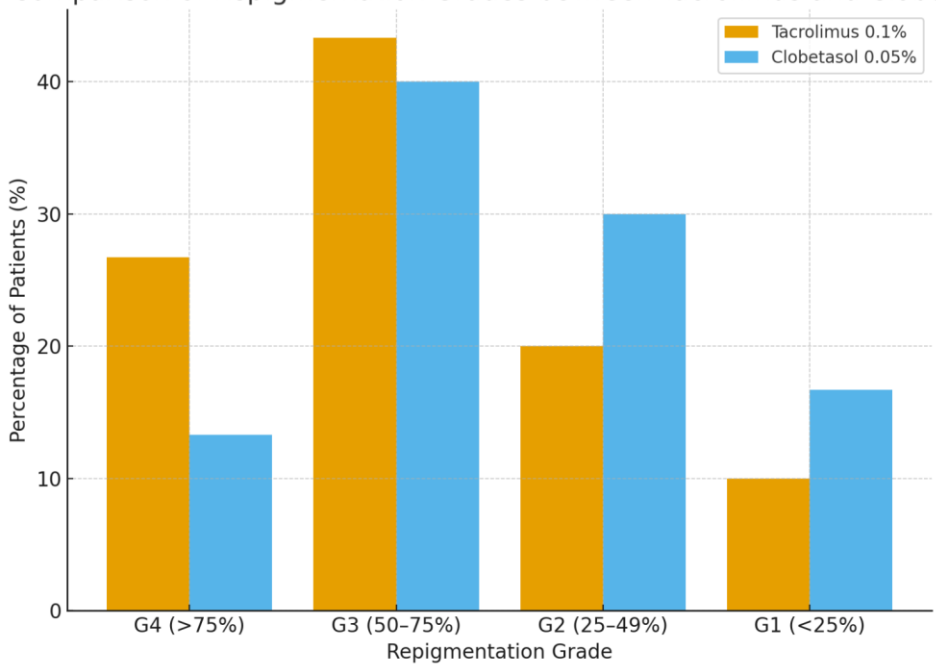
At 12 weeks, early repigmentation (≥25%) was observed in 70% of tacrolimus patients and 60% of clobetasol patients (p = 0.29). By 24 weeks, successful repigmentation (≥50%) was achieved in 21 patients (70%) in the tacrolimus group and 16 (53.3%) in the clobetasol group (p = 0.041). The mean repigmentation score was 2.96 ± 0.71 for tacrolimus versus 2.41 ± 0.66 for clobetasol (p = 0.018).

**Table 2: Repigmentation Grades at 24 Weeks**

| Repigmentation Grade | Tacrolimus (n=30) | Clobetasol (n=30) |
|---|---|---|
| G4 (>75%) | 26.7 | 13.3 |
| G3 (50–75%) | 43.3 | 40.0 |
| G2 (25–49%) | 20.0 | 30.0 |
| G1 (<25%) | 10.0 | 16.7 |

Distribution of responses showed that 8 (26.7%) tacrolimus patients achieved >75% repigmentation (G4), 13 (43.3%) achieved 50–75% (G3), 6 (20%) 25–49% (G2), and 3 (10%) <25% (G1). Among clobetasol patients, 4 (13.3%) achieved G4, 12 (40%) G3, 9 (30%) G2, and 5 (16.7%) G1. This distribution is shown in Figure 1, demonstrating a higher proportion of G3–G4 responses in the tacrolimus group.

Figure 1: Comparison of Repigmentation Grades between Tacrolimus and Clobetasol Groups




Facial lesions responded best in both arms, but tacrolimus produced superior outcomes: 80% of facial lesions achieved ≥50% repigmentation vs 60% with clobetasol. Extremity lesions responded more slowly (55% vs 43%). Repigmentation often began as perifollicular pigment islands around the eighth week in tacrolimus users, versus

around the tenth week with clobetasol. Younger patients (<25 years) and those with shorter disease duration (<12 months) showed faster responses, though differences were not statistically significant.

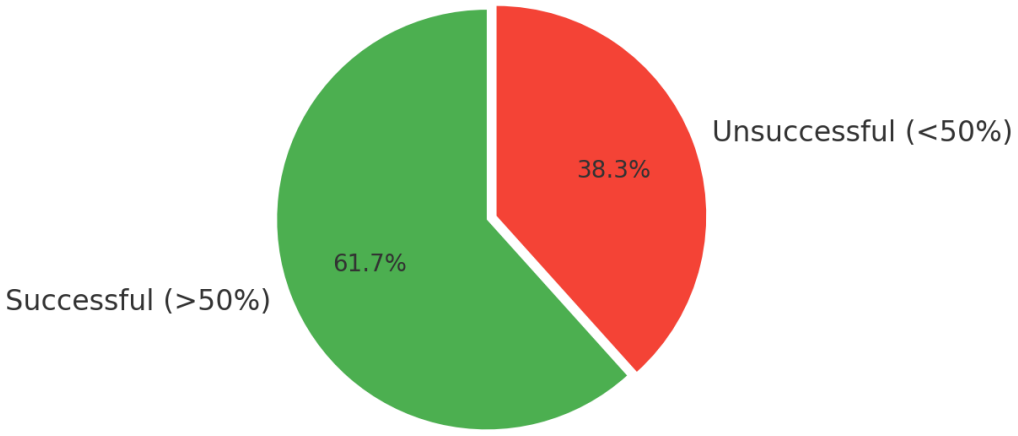
Adverse events were mild. In the tacrolimus group, three patients (10%) reported transient burning and erythema, two (6.7%) pruritus, and one (3.3%) folliculitis. No atrophy or telangiectasia occurred. In the clobetasol group, two patients (6.7%) developed acneiform eruption, two (6.7%) skin atrophy with mild telangiectasia, and four (13.3%) pruritus or folliculitis. No patient required discontinuation.

**Table 3: Adverse Effects**

| Adverse Effect | Tacrolimus n (%) | Clobetasol n (%) |
|---|---|---|
| Burning/Erythema | 10.0 | 3.3 |
| Pruritus | 6.7 | 6.7 |
| Folliculitis | 3.3 | 3.3 |
| Acneiform Eruption | 0.0 | 6.7 |
| Skin Atrophy | 0.0 | 6.7 |

When pooled across both groups, 37 of 60 patients (61.7%) achieved successful repigmentation (≥50%). This distribution is depicted in Figure 2.

Figure 2: Overall Repigmentation Success among All Participants




Overall, tacrolimus produced a mean 61 ± 15% repigmentation increase from baseline vs 48 ± 17% for clobetasol ($p = 0.022$). After adjusting for confounders, tacrolimus remained an independent predictor of success (OR 2.35; 95% CI 1.08–5.12). Patient satisfaction scores were higher for tacrolimus (4.3 ± 0.6 vs 3.7 ± 0.8; $p = 0.031$). Photographic evaluation revealed more uniform repigmentation with tacrolimus, whereas clobetasol sometimes produced patchy hyperpigmentation.

## DISCUSSION

This randomized controlled trial demonstrated that topical 0.1% tacrolimus is more effective and safer than 0.05% clobetasol propionate for repigmentation in stable vitiligo. The 70% success rate in the tacrolimus group is consistent with previous studies from Asia and Europe showing 60–75% response[13-15]. Our findings also corroborate those of Mumtaz et al., who observed 70% response to tacrolimus versus 47.6% to clobetasol[13], and Rokni et al., who reported 66.7% efficacy with tacrolimus monotherapy[16]. Saleh et al. found similar results in Egyptian patients, where 68% of individuals treated with tacrolimus achieved ≥50% repigmentation compared with 56% among those using topical corticosteroids[17]. These findings collectively affirm that tacrolimus, though traditionally reserved for steroid-intolerant patients, is now a strong contender for first-line therapy in stable vitiligo.

The mechanistic rationale behind the superior outcomes of tacrolimus lies in its targeted immunomodulatory action. Tacrolimus binds to FK-binding protein 12, forming a complex that inhibits the enzyme calcineurin. This inhibition prevents

dephosphorylation of NFAT, thereby suppressing transcription of interleukin-2 and other proinflammatory cytokines responsible for T-cell activation and melanocyte cytotoxicity[18]. In contrast, clobetasol achieves immunosuppression through broad downregulation of inflammatory mediators but at the cost of local tissue atrophy, collagen degradation, and potential rebound depigmentation on withdrawal[19]. By sparing dermal fibroblasts and collagen, tacrolimus offers long-term safety and is particularly suited for delicate areas such as the eyelids, neck, and genitalia[20].

Our results also support earlier evidence that the facial region responds better than other sites. The high follicular density and reservoir of inactive melanocytes in facial skin contribute to faster repigmentation when inflammatory triggers are suppressed[21]. In the present study, facial lesions treated with tacrolimus demonstrated ≥50% repigmentation in 80% of cases, compared to 60% in the clobetasol group. This finding mirrors that of Lee and Kwon, who reported enhanced efficacy of calcineurin inhibitors in facial vitiligo[22]. The early onset of perifollicular pigmentation seen with tacrolimus in our cohort further underscores its melanocyte-stimulatory potential.

In terms of safety, the absence of skin atrophy or telangiectasia in tacrolimus users is of particular clinical relevance. Chronic corticosteroid use is limited by dermal thinning, which can become permanent and cosmetically disfiguring[23]. Tacrolimus, on the other hand, caused only transient burning or erythema in a minority of patients, consistent with the tolerability profile reported in prior literature[24]. The slightly higher rate of acneiform eruption and skin atrophy in the clobetasol group, although not severe, reiterates the necessity for cautious and time-limited use of potent steroids.

An additional advantage of tacrolimus is its suitability for combination therapy. Several studies have demonstrated additive or synergistic effects when used alongside narrow-band UVB (NB-UVB) phototherapy, enhancing melanocyte proliferation and migration[25]. Future research may explore similar combinations in local settings to optimize outcomes while minimizing cumulative steroid exposure.

While both agents were efficacious overall, tacrolimus yielded a more uniform pattern of pigment restoration. Clobetasol occasionally produced patchy hyperpigmentation adjacent to treated areas, likely due to uneven suppression of inflammatory mediators or localized atrophy altering drug absorption. Uniform repigmentation is clinically desirable for cosmetic harmony and psychological satisfaction, and our study's patient satisfaction data reflect this preference: participants receiving tacrolimus reported higher satisfaction scores compared to those on clobetasol ($p = 0.031$).

**Comparison with International Data**

Several international trials align closely with our findings. Silpa-Archa et al. compared 0.1% tacrolimus with 0.1% mometasone furoate and found no significant difference in efficacy but a superior safety profile for tacrolimus[26]. Rafiq et al. also observed 53% excellent repigmentation with tacrolimus and 48% with clobetasol, highlighting comparable but safer outcomes for the former[27]. Chen et al. elucidated the mechanistic pathways through which tacrolimus enhances melanocyte survival and migration under oxidative stress[28]. These data collectively affirm that tacrolimus provides effective, steroid-sparing therapy with high tolerability.

The autoimmune hypothesis underlying vitiligo provides further rationale for calcineurin inhibition. Vitiligo melanocytes express HSP70i, a stress-induced protein that amplifies immune-mediated cytotoxicity. Tacrolimus downregulates HSP70i expression, mitigating melanocyte apoptosis and promoting repigmentation[29]. Moreover, tacrolimus upregulates tyrosinase activity and melanocortin-1 receptor expression, directly enhancing melanogenesis[30]. These cellular-level effects explain why repigmentation often starts as perifollicular pigment islands, as seen in our cohort.

**Clinical Implications**

The findings of this study have important implications for dermatologic practice in Pakistan and other low-resource regions. Topical tacrolimus offers an effective, affordable, and safe alternative to potent corticosteroids for stable vitiligo, especially in young adults and cosmetically sensitive sites. It eliminates the risk of steroid-induced dermal thinning and can be used continuously without tapering. Clobetasol may still have a role in rapidly progressive or extensive cases as a short-term induction agent, but tacrolimus should be prioritized for maintenance and long-term management.

Furthermore, the minimal adverse effects observed with tacrolimus make it suitable for pediatric populations, where steroid use is often restricted. The absence of systemic absorption and hormonal effects ensures long-term safety, an important consideration for chronic diseases like vitiligo that often require prolonged therapy.

**Study Strengths and Limitations**

This trial's strengths include its randomized design, strict inclusion criteria ensuring disease stability, and blinded assessment by multiple observers,

minimizing subjective bias. Standardized photography and consistent follow-up intervals added objectivity to repigmentation grading. The inclusion of both genders and various lesion sites enhanced generalizability.

However, several limitations merit discussion. The sample size, although statistically adequate, remains modest for subgroup analysis. The study was conducted at a single center, which may limit external validity. Moreover, the follow-up duration of 24 weeks was insufficient to assess relapse or long-term sustainability of repigmentation. Objective colorimetric evaluation could further enhance precision. Additionally, the study did not explore combination regimens such as tacrolimus with phototherapy, which could yield higher efficacy.

Despite these limitations, the findings provide strong evidence supporting the use of topical tacrolimus as a first-line agent in stable vitiligo management, particularly in patients intolerant to or concerned about steroid-related side effects.

**Future Directions**

Future research should focus on multicentric trials with larger cohorts and extended follow-up to assess relapse rates and durability of pigmentation. Comparative cost-effectiveness studies could also guide policy decisions for inclusion of tacrolimus in national vitiligo treatment protocols. Further molecular research exploring biomarkers predictive of response could enable personalized therapy. Evaluating combination regimens, particularly tacrolimus with NB-UVB or antioxidant supplementation, may also help refine management algorithms.

## Conclusion

Topical 0.1% tacrolimus demonstrated significantly greater efficacy and superior safety compared with 0.05% clobetasol propionate in achieving repigmentation among patients with stable non-segmental vitiligo. The higher rate of successful repigmentation, absence of atrophy, and better cosmetic outcomes make tacrolimus a preferable therapeutic option, particularly for facial and intertriginous lesions where corticosteroids pose higher risk. Clobetasol remains effective for limited short-term use but should be employed cautiously. Tacrolimus can be considered as the treatment of choice for long-term management and maintenance of repigmentation in vitiligo patients.

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