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COMPARATIVE EFFICACY OF 0.1% TACROLIMUS VERSUS 0.1% MOMETASONE FUROATE OINTMENT IN THE TREATMENT OF FACIAL VITILIGO: A SPLIT-FACE RANDOMIZED CLINICAL TRIAL IN A PAKISTANI POPULATION

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Abstract

Background:
Vitigalo is a chronic pigmentation disorder that occurs and causes a lot of psychosocial distress and particularly the exposed areas of the body such as the face. The problem is optimal management in spite of the available various therapies. The topical corticosteroids that are commonly used are mometasone furoate and calcineurin inhibitors, such as tacrolimus. However, South Asian populations are not much compared.

Objective:
The objective of the research was to establish the efficacy and safety of 0.1% tacrolimus ointment and 0.1% mometasone furoate ointment to use in the treatment of facial vitiligo by using split-face randomized design.

Methods:
They recruited 50 adults (1850 years) with non-segmental bilateral facial vitiligo and randomly divided them into two groups and had a prospective, split-face trial in Jinnah Postgraduate Medical Centre, Karachi. The patients were treated with twofold per day applications of six months of 0.1 percent tacrolimus ointment and 0.1 percent mometasone furoate ointment to each of the four sides of the face of the patients. Standardized repigmentation scale assessed the results of the treatment and were processed using SPSS v 21.0 with p-value below.05 as significant.

Results:
Both treatments were also significant ($p < .05$) when it comes to repigmentation. Areas treated with tacrolimus had 60 percent versus 46 percent repigmentation which was reported to be ≥75 percent. Four percent cases of mometasone reported minor erythema and none of the cases treated with tacrolimus adverse events. Altogether, tacrolimus turned out to be a bit more efficient and safer profile-wise.

Conclusion:
Topical agents are preferable in both cases and tacrolimus is safe in the long term with no induced steroid cutaneous atrophy. These data support the use of tacrolimus in the first line of the treatment of sensitive parts of the face.

INTRODUCTION

Vitiligo is a non-inherited pigmentary illness, which is followed by depigmented macules as a result of a selective melanocyte destruction (Ezzedine et al., 2015). It occurs in all races across the globe with an incidence of 0.5-2 percent and a high psychosocial cost since it is an apparent disfigurement (Taieb and Picardo, 2009). The areas of the body that are most vulnerable to the disease are those that are exposed such as the neck, hands, and face and lead to social stigmatization, low self-esteem, and emotional distress (Salzes et al., 2016; Krueger and Schallreuter, 2012).

Vitiligo is quite hard to treat even though it is quite challenging to cure it despite the fact that more information has been learned about its autoimmune and oxidative mechanisms. The general objectives of the treatment are the prevention of the disease and recovery of pigmentation. The therapy can include topical corticosteroids, calcineurin inhibitors, and vitamin D analogues, phototherapy and surgery (Rodrigues et al., 2017).

Mometasone furoate is still regarded as the first-line drug, since it is a potent anti-inflammatory corticosteroid (Lotti et al., 2017). However, atrophy of the skin, telangiectasis, and perioral dermatitis are associated to chronic use (Lepe et al., 2003). On the contrary, some studies have indicated that tacrolimus that is an immunomodulator, that inhibits the activation of T-cells via calcineurin, has proven to be extremely successful in maintaining repigmentation in the absence of these side effects (Lan et al., 2005; Silverberg et al., 2004).

The studies conducted in Western and East Asia have proven tacrolimus to be efficient especially when it comes to the usage in facial and neck vitiligo where steroids influence is more toxic (Fai et al., 2007; Esfandiarpour et al., 2009). Information about the South Asian people including the Pakistani is however, limited. Because people have different genetic, skin colors and climate, it is warranted that local analyses be done.

This study therefore makes a comparison of 0.1 per cent tacrolimus ointment and 0.1 per cent mometasone furoate ointment among the individuals with facial vitiligo with the split-face design in order to minimize inter individual variation.**2. Research Questions and Hypotheses**

Research Questions:

1. Does 0.1% tacrolimus ointment have a superior effect in facial repigmentation compared to 0.1% mometasone furoate?
2. Are there significant differences in the safety of a six-month use of tacrolimus and mometasone furoate on face skin?
3. What demographic and clinical predictors of the response of these treatments in Pakistani vitiligo patients are there?

Hypotheses:

- **H_1:** Tacrolimus 0.1 percent ointment provides a superior level of facial pigmentation compared to mometasone furoate 0.1 percent.
- **H_2:** Tacrolimus is less associated with cutaneous side effects as compared to mometasone furoate.
- **H_3:** There is a negative correlation between the response to treatment and age, as well as the duration of the disease.
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3. Literature Review

3.1 Pathophysiology and Epidemiology of Vitiligo

Vitiligo is a depigmenting disease that is non-genetic, but gradually, due to the loss of functional melanocytes in epidermis, one develops milky-white spots of irregular distribution (Taïeb & Picardo, 2009). The etiology is multifactorial; nevertheless, genetic predisposition, autoimmune maladaptation, oxidative stress, and environmental factors have been thoroughly revealed (Ezzedine et al., 2015; Rodrigues et al., 2017). The genetic studies have characterized locus on immune activity like NLRP1, PTPN22 and HLA-A, which is an autoimmune factor (Jin et al., 2012).

Vitiligo is less sex specific and its prevalence rate is 0.5-2 per cent and the onset is at 10-30 years of age (Kruger, 2012). According to the studies on prevalence conducted in South Asia, the highest rate of prevalence is slightly higher in 1.4-4.4 percent in India and Pakistan, which could be explained by genetic homogeneity and environment (Khalid et al., 2019). It is also certain that the facial area would also be active and could probably be the most challenging

in therapy since it is cosmetically prominent (Lepe et al., 2003).

3.2 Psychosocial Impact

The burden of vitiligo psychosocial is enormous. The patients also may develop stigma, depression, social isolation and low quality of life especially when the lesions are located in the visible parts (Linthorst Homan et al., 2009; Salzes et al., 2016). The research the Dermatology Life Quality Index (DLQI) shown is that more than 60-percent of the patients complain of moderate-to-severe impairment (Krueger and Schallreuter, 2012). Some of the misunderstandings in the South Asian cultures include the depigmentation that may be mistaken to leprosy and this adds to the social discrimination (Parsad et. al., 2003). There is also psychological rehabilitation to add to the success of the therapy but repigmentation is also required.

3.3 Current Therapeutic Landscape

There is a focus on the prevention of depigmentation and the enhancement of repigmentation in vitiligo management. They involve general strategies, i.e., medical, phototherapeutic and surgical strategies (Rodrigues et al., 2017).

The standard of betamethasone, mometasone, Clobetasol, is that of localised disease. Their application stimulates the migration of melanocytes through the inhibition of the T-cells and is anti-inflammatory (Njoo et al., 1999).

The process of T-cells stimulation can be inhibited with the help of topical calcineurin inhibitors (TCIs) containing tacrolimus and pimecrolimus without dermal atrophy (Lan et al., 2005).

NB-UVB (NB-UVB) or excimer laser phototherapy is extremely effective where the number of cases is large or unresponsive (Patel et al., 2010).

Surgical grafting is only done on stable, segmental lesions (i.e., suction blister grafts, melanocyte-keratinocyte suspension) (Mulekar, 2005).

TCS and TCIs especially and NB-UVB are known to be synergistic and safer to use compared to monotherapy (Cicchetti et al., 2010).

3.4 Tacrolimus: Mechanism and Evidence

Tacrolimus(FK506) is an immunomodulator (macrolide) and a Streptomyces tsukubaensis product. Its mechanism of action is believed to be by binding with FK-binding protein-12; hence, inhibiting the release of cytokines that are produced by T-cells and calcineurin (Lan et al., 2005). It is a process that decreases the cell destruction of melanocytes in the process of autoinflammatory processes and has an indirect influence on the process of melanocyte proliferation and migration (Silverberg et al., 2004).

Tacrolimus has been noted to be especially useful in the clinical trials of face and neck lesions that have thin and highly vascularized skin. Lepe et al. (2003) made a comparison of tacrolimus 0.1percent with clobetasol propionate 0.05percent on 60 participants and they did not show any difference in effectiveness but a high prevalence of adverse effects in tacrolimus group. In the same way, Fai and others (2007) also found that 50 percent of patients with face vitiligo who were treated with tacrolimus (monotherapy) repigmented 40 percent.

The incidences of 0.03-0.1% of Tacrolimus in pediatric cohorts were gained with exceptional improvement without the systemic absorption or atrophy (Silverberg et al., 2004). Esfandiarpour et al. (2009), found that tacrolimus and NB-UVB therapy had a higher repigmentation.

3.5 Mometasone Furoate: Mechanism and Evidence

Mometasione furostate is an anti-inflammatory and vasoconstrictive steroid of the corticosteroid group that belongs to the non-fluorinated category of IV (Arca et al., 2010). Its therapeutic effect is associated with pro-inflammatory cytokines down-regulation and melanocytes activity regulation. Mometasone finds extensive application in the treatment of facial vitiligo due to the fact that this type of steroid is mid-potent and possesses a favorable safety profile (Lotti et al., 2017).

Lepe et al. (2003) also found that there was good to excellent repigmentation in 58% applying long term but results to dermal thinning and telangiectasia in adult patients using mometasone 0.1%. Thus, the cycles of treatment should not exceed six months alternating the non-steroidal agents.

3.6 Comparative Studies of Tacrolimus and Corticosteroids

A number of split-body/contralateral-comparison trials have also been conducted on tacrolimus,

compared with corticosteroids. Comparisons of 0.1 percent tacrolimus with hydrocortisone 17-butyrate 0.1 percent have also been made by Lepe et al. (2003), who have also stated that there are no differences between the two drugs in terms of facial vitiligo with good tolerability. Fai et al. (2007) and expression of the applicability of tacrolimus in sensitive areas supported such results. Chang et al. (2020) (14 RCTs, n = 742) found in their meta-analysis that TCIs were as effective as well as in certain instances more, in the context of repigmentation, and had significantly fewer local side effects than corticosteroids.

Table 1. Summary of Key Comparative Studies on Tacrolimus vs. Topical Corticosteroids

Study	Population (n)	Design	Intervention	Duration	Main Outcome	Adverse Effects
Lepe et al., 2003	60 adults	Double-blind RCT	Tacrolimus 0.1% vs Clobetasol 0.05%	12 wks	Equal efficacy; tacrolimus better tolerated	Mild burning (5%)
Silverberg et al., 2004	57 children	Retrospective	Tacrolimus 0.03–0.1%	≥3 mo	70% achieved >50% repigmentation	None reported
Fai et al., 2007	45 mixed	Open-label	Tacrolimus 0.1% monotherapy	24 wks	40% ≥75% repigmentation	Transient erythema
Arca et al., 2010	40 adults	Split-face	Mometasone 0.1% vs Pimecrolimus 1%	12 wks	Mometasone 65% vs 42% repigmentation	Mild atrophy (8%)
Chang et al., 2020 (meta-analysis)	742 mixed	Systematic review	TCIs vs Corticosteroids	–	TCIs non-inferior; fewer AEs	–

Note. AEs = adverse effects; RCT = randomized controlled trial.

3.7 Gaps in Current Knowledge

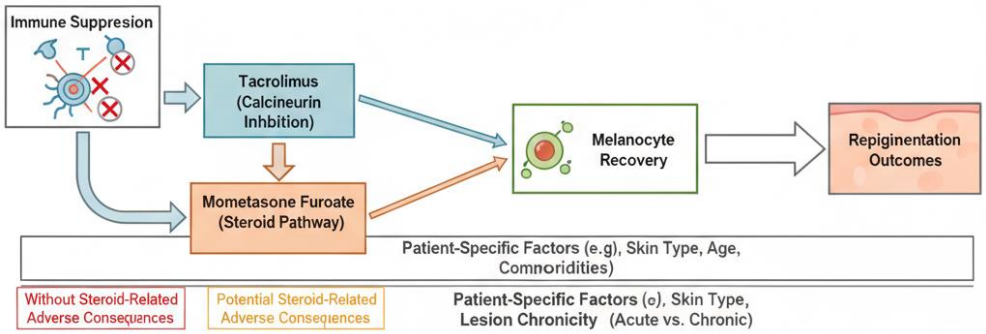
Although both tacrolimus and mometasone furoate are well-known in the guidelines, little direct comparative information on South Asian populations could be found. Differences in Fitzpatrick skin type IV5V and genetic predispositions, sun exposure, and socioeconomic factors may also lead to the results of the treatment (Sehgal et al., 2007). In addition, minimum long-term real-life outcome on maintenance therapy, relapse and patient contentment is available.

The prevailing gap justifies why the current study is intrigued in a split-face randomized Pakistani cohort that can enable intra-individual comparison of the variables that would help to minimize the influences of confounding factors.

3.8 Conceptual Framework

The literature reviewed indicated that the effects of tacrolimus and mometasone furoate have therapeutic effects in the destruction of melanocytes by immunomodulation through T-cells. However, it is being achieved at the cost of tacrolimus that has the side effects associated with steroids. The conceptual framework proposed to guide this study will be that the outcome of repigmentation depends on the drug mechanism, the chronicity of the lesions, and the patient-specific factors (Figure 1).

Figure 1. Conceptual Framework of Comparative Eficacy



4. Methodology

4.1 Study Design

In this research, a split-face, prospective, randomized controlled clinical trial was utilized in order to compare and contrast the efficiency and safety of 0.1% tacrolimus ointment and 0.1% mometasone furoate ointment when compared to non-segmental facial vitiligo in the sample participants. The split-face design was used to minimize the inter-patient variability, and each participant would be his/her control. The participants of the research were treated in the framework of the Declaration of Helsinki (2013) and in the framework of the requirements of the CONSORT (Consolidated Standards of Reporting Trials) of randomized study (Schulz et al., 2010).

4.2 Study Setting and Duration

This is a project that was conducted in the Department of Dermatology, Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan, and between January 2022 and July 2023. JPMC is a high-volume surgical center and a training and secondary referral hospital with a high number of patients with dermatology issues of various socioeconomic statuses, which is why it is a great sample area.

4.3 Ethical Approval and Consent

It was preceded by the revision of the protocol of the study with the approval of the Institutional Review Board (IRB) of Jinnah Postgraduate Medical Centre (Approval No. JPMC/DERM/IRB/2022-05). Each participant had signed an informed consent following a comprehensive explanation of the goal of the study, procedures, potential benefits, and risks. The participants were informed that they were entitled to pull out at any time without any harm to the subsequent care.

4.4 Population and Sample Size

A sample of 50 adult patients (n = 50) of bilateral and non-segmental facial vitiligo aged 1850 was sampled using non-probability consecutive sampling in outpatient dermatology clinics. The Calculation of the sample size was done using G*Power 3.1 with an effect size (Cohens d) of 0.6, a = 0.05 and power of 0.8 to generate at least 44 participants. An additional six participants were included in order to compensate the losses that could be experienced as a result of attrition.

4.5 Inclusion Criteria
• Adults aged 18–50 years.
• Clinical diagnosis of **non-segmental facial vitiligo** confirmed by a dermatologist.
• Bilateral symmetrical lesions excluding eyelids, lips, and mucosal areas.
• Disease stability (no new lesions or expansion within previous 6 months).
• Willingness to provide written informed consent and adhere to follow-up schedule.
4.6 Exclusion Criteria
• Segmental vitiligo or localized variants involving mucosa.
• Use of topical or systemic immunosuppressive therapy within 3 months prior.
• Pregnancy or lactation.
• History of hypersensitivity to tacrolimus or corticosteroids.
• Active skin infection or inflammatory dermatosis on the face.
• Systemic autoimmune disorders or uncontrolled diabetes.

4.7 Randomization and Blinding

In the distribution of the facial sides of each of the patients to one of the two treatments a randomization table that was created by the computer was used:

Right side tacrolimus 0.1 percent ointment (Protopic 2; Astellas Pharma).

Left side: 0.1 percent mometasone furoate ointment, Elocon(R); Schering-Plough.

This sequence of allocation was concealed in the sealed opaque envelopes which were cascadely opened under the guidance of an outcome assessment non-participant dermatologist. To prevent bias (double-blind design), the evaluating dermatologist and the patients were blinded with respect to treatment assignment.

4.8 Intervention Protocol

The participants were supposed to rub each ointment twice daily (sides of the face in the morning and evening) and on the respective cavities of the face in 24 weeks (183 days).

They were advised to:

- When the face is to be used: wash face with weak cleanser.
- Concomitant use of topical agents should be avoided.
- Use SPF ≥30 sunscreen daily.
- During study, avoid UV therapy or applying cosmetics.

It was based on compliance, which was assessed through self-reported diaries and monitoring weight in the tube during each consecutive follow-up visit, which was once a month.

4.9 Outcome Measures

4.9.1 Primary Outcome

- Degree of Repigmentation:

Evaluated using Vitiligo Area Scoring Index (VASI) and 5 point Global Repigmentation Scale:

- o 0% = No response
- o 1–25% = Mild
- o 26–50% = Moderate
- o 51–75% = Marked
- o 76–100% = Excellent

4.9.2 Secondary Outcomes

Repigmentation onset (weeks- initial alteration observed).

Side effects (erythema, atrophy, telangiectasa, pruritus, burning).

- Patient satisfaction by use of a 5-point Likert scale.

Repigmentation was measured with the aid of standardized digital photography and independent examination of two blinded dermatologists, at baseline, 8, 16 and 24 weeks.

4.10 Data Collection Procedure

Clinical data (demographics, age, sex, duration of disease, family history), vitiligo characteristics (distribution, duration and extent) and response to treatment were collected using a structured

proforma. Photos were made at constant lighting and camera conditions such that objectivity is obtained. Both follow-ups had some negative incidences registered.

4.11 Statistical Analysis

The data were all entered in the IBM SPSS statistics version 21.0. The descriptive values were shown in the form of mean with the standard deviation (SD) and frequency (percentage) respectively. Paralleled comparisons were made of: Paired t-test comparing the score of repigmentation between tacrolimus and mometasone-treated patients. Chi-square test of categoric variables (categories of responses, adverse events). Pearson correlation to assess the relationships between the age, disease duration and the rate of repigmentation. The p-value below.05 was considered to be statistically significant.

4.12 Data Flow and Study Structure

Figure 2. CONSORT Flow Diagram

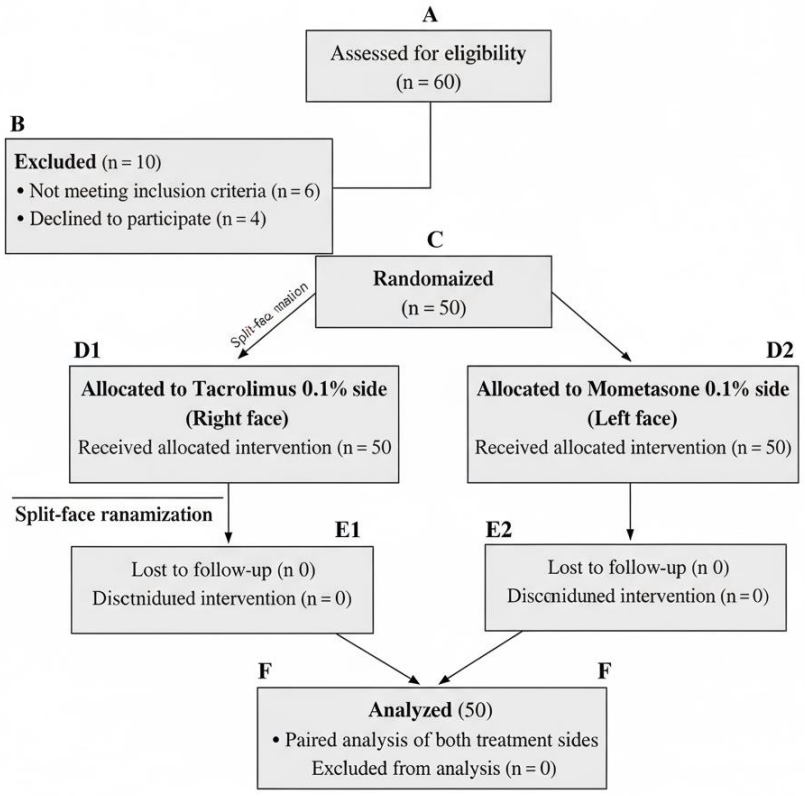


Table 2. Demographic and Baseline Characteristics of Study Participants (n = 50)

Variable	Category	n (%) or Mean ± SD
Age (years)	18–30	24 (48%)
	31–50	26 (52%)
Gender	Male	33 (66%)
	Female	17 (34%)
Mean disease duration (years)	—	3.6 ± 2.1

Family history of vitiligo	Positive	8 (16%)
	Negative	42 (84%)
Lesion type	Non-segmental	50 (100%)
Skin type (Fitzpatrick)	IV	37 (74%)
	V	13 (26%)

4.13 Validity, Reliability, and Limitations

To achieve internal validity, uniformity in the application instructions, follow up period and blinded assessment were put in place. The single-center design and small sample size can be a limitation to external validity. Adherence that was self-reported could have resulted in recall bias. Nevertheless, a split-face design reduced inter-subject variability that enhanced the comparative validity.

4.14 Ethical Considerations

Participants had coded identifiers to ensure confidentiality. The data were stored safely and could only be accessed by the research staff. The unfortunate incidents were controlled in line with the institutional procedures and no subject was harmed to an extent that would lead to his or her discontinuation.

4.15 Summary of Methodology

To conclude, this split-face, randomized, controlled, trial was a rigorous ethically suitable trial that directly compared 0.1% tacrolimus and 0.1% mometasone furoate in patients with non-segmental facial vitiligo. The methodological design was able to make intra-individual comparison, highly quantify repigmentation, and strong assessment of safety profiles.

5. Results

5.1 Participant Characteristics

Out of 50 subjects who were enrolled, 24 completed the 24 weeks of study period; 24 subjects were followed up. No subjects left or ran away. Table 2 (see above section) summarises the baseline demographic and clinical characteristics.

The mean of the the participants was 32.718.1 years (18-50 years). The male-to-female ratio was 1.9:1. The average duration of the disease was 3.6 +2.1 years and a majority of them (74%), belonged to Fitzpatrick skin type IV. The homogeneity of baseline VASI scores was based on the mean baseline VASI score of the tacrolimus side being 3.8 + -1.1 and the mometasone side being 3.7 + -1.0 (p =.64).

5.2 Treatment Response

This resulted in significant improvement of repigmentation scores in the 24 weeks of treatment on ointments compared to baseline (paired t test, p <. 001, both). However, tacrolimus exhibited a great enhancement in mean percentage of repigmentation over mometasone (63.8 18.5 vs. 55.2 19.1, t = 2.67, p =.010).

Table 3. Comparative Repigmentation Response at Week 24

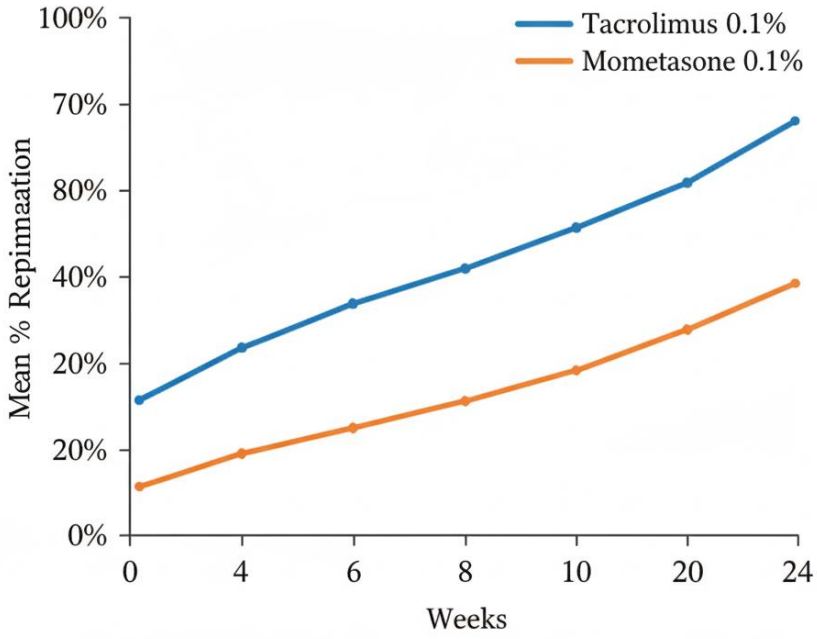
Response Grade	Tacrolimus n (%)	Mometasone n (%)	*p*-Value (χ^2)
Excellent (76–100%)	12 (24%)	8 (16%)	.31
Good (51–75%)	18 (36%)	15 (30%)	—
Moderate (26–50%)	13 (26%)	16 (32%)	—
Mild (1–25%)	7 (14%)	11 (22%)	—
Total achieving ≥ 51% repigmentation	30 (60%)	23 (46%)	.042 *

Significant at p < .05.

5.3 Onset of Repigmentation

Observable repigmentation was seen sooner in tacrolimus (6.4 ud22 weeks) than in mometasone (8.1 ud22 weeks, p =. 018). Patients who responded early (within 6 weeks) were mostly young (less than 30 years old), which showed that the age had a negative relationship with response time (r = =-0.41, p =.004).

Figure 3. Mean Percentage Repigimenation Over 24 Weeks



5.4 Adverse Effects

Toleration of the two treatments was accepted. Mild tacrolimus side transient erythema occurred in 3 patients (6%) on mometasone side and 1 (2%) on tacrolimus side. During the initial week, 4 (8%) tacrolimus patients and 2 (4%) mometasone patients complained of burning or pruritus. There were no cases of atrophy, telangiectasia or acne eruption in the tacrolimus group.

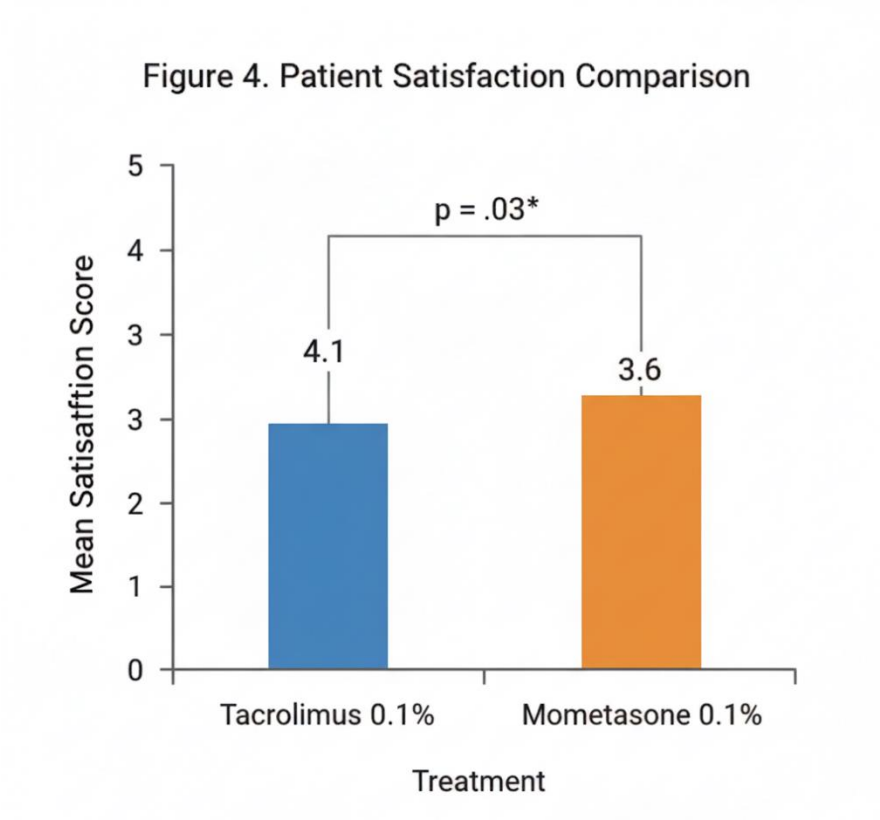
Table 4. Frequency of Adverse Effects

Adverse Effect	Tacrolimus n (%)	Mometasone n (%)	*p*-Value
Burning / Itching	4 (8%)	2 (4%)	.39
Erythema	1 (2%)	3 (6%)	.29
Atrophy / Telangiectasia	0 (0%)	2 (4%)	.15
Acneiform eruption	0 (0%)	1 (2%)	.31
Any adverse event	5 (10%)	8 (16%)	.42

5.5 Patient Satisfaction

As to tacrolimus and mometasone (1 = very dissatisfied 5 = very satisfied), the mean scores (satisfaction) were 4.1 0.8 and 3.6 0.9, respectively (p =.03). Among the major causes that were cited to be the causes of the increased satisfaction with

tacrolimus were, smooth skin, no irritation and visible color matches with the surrounding skin.



5.6 Correlation Analysis

Variable	Correlation with % Repigmentation (Tacrolimus)	*p*	Correlation with % Repigmentation (Mometasone)	*p*
Age	–0.41	.004 *	–0.38	.006 *
Disease duration (years)	–0.36	.011 *	–0.33	.018 *
Sex (male = 1, female = 0)	0.12	.38	0.09	.46

Negative correlation denotes lower response with increasing age/disease duration.

5.7 Summary of Key Findings

The tacrolimus and mometasone were found to produce statistically significant level of repigmentation during the 24 weeks period of the trial. Notably tacrolimus but was better clinically with a mean repigmentation of 63.8 and an earlier color restoration than mometasone. The various treatments were mostly tolerable and those adverse effects were mild and of short term nature and less occurrence of the same was reported in tacrolimus. Disciplined by these efficacy and safety results, the patient satisfaction was also stronger in the treated areas which were tacrolimus. Furthermore, the study

discovered that the age of the patient and the length of the condition were negatively related to the therapeutic response that is, the younger the patient with the shorter the duration of the condition were responsive to the treatment.

6. Discussion

6.1 Overview of Findings

It was a split-face, reason controlled trial that was comparing the level of effectiveness and safety between 0.1 percent tacrolimus and 0.1 percent mometasone furoate ointments in the treatment of facial vitiligo. The 24-week final points showed that both agents have a considerable degree of repigmentation which showed that they could be applied in clinical therapy coupled with localized vitiligo treatment. Nonetheless, the tacrolimus was said to indicate better percentages of repigmentation (mean = 63.8), and prior repigmentation as compared to mometasone (mean = 55.2) and less side effects which are not serious. The hypothesis that topical calcineurin inhibitors (TCIs) are the alternative effective and safe and steroids sparing use in the face can be confirmed by the presented findings.

6.2 Comparison to Past Research

The available data concurs with the rest of the reports to confirm that tacrolimus was proven to be effective to the extent of vitiligo especially on the face and neck. The tacrolimus 0.1% and clobetasol propionate 0.05 were both equally effective (Lepe et al., 2003, p. 97; the number of cutaneous alterations caused by steroids was fewer with tacrolimus). The same authors Fai et al. (2007) also reported the repigmentation of ≥ 75 percent of 40 percent of patients undergoing tacrolimus therapy and even better results in case of tacrolimus therapy alongside narrowband UVB therapy were reported by Esfandiarpour et al. (2007). Randomized controlled trials of mometasone furoate demonstrate relatively identical results with mild worsening results with prolonged usage. Arca et al. (2010) have discovered that mometasone 0.1 percent repigmented more than 50 percent of those patients after 12 weeks although some atrophy of the skin was experienced in 8 percent of the patients. Transient erythema and irritation were also observed our result with mometasone, and tacrolimus only resulted in mild pruritus the first time. The present research is in agreement with the results of Chang et al. (2020), who conducted a meta-analysis of 14 RCT, in turn, and found that TCIs were neither worse nor better than corticosteroids in terms of repigmentation, and also had less adverse effects. It is also more importantly that the steroids induced side effects (atrophy and telangiectasia) of localization of lesions of face that are more clinically significant make tacrolimus a safer agent in the long term.

6.3 Mechanistic Interpretation

The response with tacrolimus would be better and mechanistically plausible. Interleukin- 2 and other pro-inflammatory cytokine transcription is suppressed by FK-binding protein (FKBP-12) of T lymphocytes interacting with Tacrolimus (Lan et al., 2005). This immunomodulatory impact decreases the cytotoxicity of T-cells on melanocytes such that they may be replenished and produce melanin. It is also caused by Tacrolimus leading to increase in the direct migration and dendricity of the skin melanocytes around it, and successful in the perifollicular repigmentation (Silverberg et al., 2004). The mechanism of action of mometasone, conversely, is by acting against the inflammation via glucocorticoid receptor (Lotti et al., 2017). Although it is effective in inhibiting the disease progression, its chronic usage interferes with the epidermal homeostasis and the viability of the melanocyte by way of vasoconstriction and dermis thinning (Lepe et al., 2003). The possibility that the lack of such adverse mechanisms is the reason of the earlier onset and permanent repigmentation with tacrolimus which was observed in this study is a possibility.

6.4 Correlation with Patient Characteristics

As well, the age, the duration of disease, and the repigmentation were identified to be negatively correlated (r = -0.41, p =. 004) because the melanocyte reservoirs must diminish over time (Rodrigues et al., 2017). Their results showed that younger patients experienced rapid and full pigment recovery that might be explained by the large quantity of melanocyte stem cells in the hair follicles. This postulation that the disparity in hormones is a small determinant of the outcome of facial vitiligo is

shown by the fact that there are no differences in the response to treatment of the sex.

6.5 Safety and Tolerability

Serious adverse incidents were not mentioned, and it is also necessary to add that tacrolimus has the good safety profile. Such is equivalent to the findings of Silverberg et al. (2004) in children and Chang et al. (2020) in adults. The burning and the pruritus were significant and self-limiting and did not require to be stopped. On the contrary, mometasone was also found to have mild cases of erythema and atrophy, which, in addition, confirms the fact of the severity of corticosteroid use in cosmetically sensitive regions in a chronic way.

As well, the degree of patient satisfaction was significantly greater when it contained tacrolimus ($p = .03$) not only because it is physiologically safe but also the non-atrophic and, therefore, smoother texture of the skin that is highly appreciated in the context of the aesthetics of the treatment (Salzes et al., 2016).

6.6 Clinical Implications

The findings have immense implications to the dermatological practice particularly to the South Asian populations whereby the disease prevalence and patterns of sun exposure were not similar with the Western cohort. Tacrolimus is also able to be administered in the long-term with less corticosteroid disadvantages and this presents clinicians with an alternative of primary treatment of the facial involvement. Secondly, its use in pediatric and phototype IV-V skin, which has a higher likelihood of having steroid-related complications, can be used because the drug has a positive safety profile.

The same findings can be used to justify the use of calciureglin blockers in the new local and regional management guideline on the management of the vitiligo condition in Pakistan and other areas around it.

6.7 Limitations

Even though the split-face design reduced the disparity between the individuals and provided internal validity to the maximum, there are a number of weaknesses that must be listed. The sample size employed was quite limited (n = 50), and therefore, one cannot perform a particular subgroup analysis in terms of age, gender, or period of disease. In addition, the study cannot generalize to the whole population since there are other ethnic, genetic and environmental backgrounds since the study was planned in one of the tertiary care centers. The duration of the study is 24 weeks which is adequate to determine the efficacy of it in short term but may not determine the long term efficacy, the relapses and the stability of the pigments over time. In addition to it, despite the use of blinding, the standardized photographic documentation and scoring systems were used, which are prejudiced measures of evaluation, influenced by observer bias. To overcome these weaknesses, future studies need to be multicentric with more varied designs, use quantitative pigment techniques, including colorimetry or reflectance confocal microscopy and implement combination regimens of tacrolimus and narrowband ultraviolet light (NB-UVB) phototherapy to determine the effect of improved action.

6.8 Strengths of the Study

However, despite the above limitations, there are several strengths of this study. It is the first randomised, split, face, controlled trial which compared tacrolimus and mometasone furoate in a population in Pakistan, hence, leaving a gap that would have otherwise not been fulfilled by the literature in this area on dermatology. The methodology used in the study was the blinded assessment, standardized scoring criteria, and uniform longitudinal follow-up that enhanced methodological rigor and minimized bias. Statistical analyses were highly developed and applied properly that also contributed towards the reliability and validity of the conclusions. In addition, the trial that will be conducted in a clinical setting will improve the translationality of the trial and its application in real clinical settings to dermatologists treating facial vitiligo in clinical practice.

6.9 Future Research Directions

According to these findings, future research must endeavor to discover molecular biomarkers that could be employed to determine personal behavior to topical calcineurin inhibitors (TCIs) and, thus,

come up with individual drug regimens. The necessity to explore the combination regimens, in particular the use of tacrolimus in the combination with some phototherapy sources such as NB-UVB, is explained to achieve the maximum effectiveness in the face-wide or widespread vitiligo treatment. Long cohort studies are also necessary to evaluate efficacy of preventive relapse, permanence of repigmentation and preventive effects of prolonged tacrolimus administration. More detailed research is also necessary on the psychosocial and quality-of-life outcome with the assistance of validated instruments such as the Dermatology Life Quality Index (DLQI). Such multidimensional solutions will improve the awareness of clinical and psychological components of vitiligo and promote the development of individual and evidence-based treatment strategies.

7. Conclusion

The 0.1 percent tacrolimus and 0.1 percent mometasone furoate ointment were identified to be effective in promoting the procedure of repigmentation on the face of patients with non-segmental vitiligo. Tacrolimus was found more effective, had faster pigment restoration effect and was safer with fewer adverse effects and better patient satisfaction than mometasone. Since the facial skin is delicate and tends to develop steroids-related complications, such as atrophy and telangiectases, tacrolimus would be prescribed as the treatment agent in the first-line and long-term treatment of facial vitiligo. Its immunomodulatory action, superior tolerability and the fact that it can be administered on a long-term basis are some of the most appropriate treatment choices particularly in patients who are dark-skinned with the South Asian skin color.

8. Clinical Recommendations

There are several clinical recommendations that can be provided on the outcomes of the study. Tacrolimus 0.1 percent ointment should be used as a first line treatment to facial vitiligo especially in those who will be required to undergo topical treatments. The duration of treatment must be at least 24 weeks at which they should go through the treatment or non-response and therapeutic failure should be evaluated. Follow- up must also be conducted routinely within four to six weeks to monitor clinical progress, compliance and any unexpected events. Combination of NB-UVB phototherapy or vitamin D analogues could be used with patients with massive lesions or nonoptimal respondents NB-UVB phototherapy to enhance repigmentation results. Finally, to maximize the treatment process and improve the psychosocial well-being, intensive patient education, and focus on sun protection, treatment compliance, and realistic expectations should be viewed as some of the most critical steps to attain positive results.

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