https://doi.org/10.29309/TPMJ/2024.31.07.7984

The Professional Medical Journal
www.theprofesional.com
2024, Volume, 31 Issue, 07

ORIGINAL ARTICLE

Microneedling plus tacrolimus versus tacrolimus alone in conjunction with narrow band UVB in the treatment of vitiligo; A randomised control trial.

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Article Citation: Afzal T, Khalid T, Inam F, Bajwa B, Goraya SI, Ahmad S, Ahsan M. Microneedling plus tacrolimus versus tacrolimus alone in conjunction with narrow band UVB in the treatment of vitiligo; A randomised control trial. Professional Med J 2024; 31(07):1119-1124. https://doi.org/10.29309/TPMJ/2024.31.07.7984

ABSTRACT… Objective: To compare the efficacy of microneedling plus Tacrolimus with narrow band UVB versus tacrolimus with narrow band UVB in the treatment of vitiligo. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Dermatology, Madinah Teaching Hospital, Faisalabad. **Period:** 05-06-2023 to 5-12-23. **Methods:** Enrolled 28 patients with stable Vitiligo for the last 3 months, aged 15 to 60 years. Patients were assigned to group A and B, treated with microneedling plus topical tacrolimus 0.1% with narrow band UVB and tacrolimus ointment twice a day. The study focused on evaluating the repigmentation response during subsequent follow-up visits, using a comprehensive four-grade scale. The results were analyzed using SPSS 26. **Results:** The study involved 34 patients with face lesions. Six patients lost follow-up and were excluded. The study included 16 males and 12 females, with a mean age of 29.4 + 11 years. After the treatment, the first follow-up visit showed significant improvement in 17 of 28 patients (60.7%) in group A (microneedling pus Tacrolimus with narrow band UVB) compared to 32.1% in group B (Tacrolimus with narrow band UVB). The efficacy was categorized into five levels: 'excellent' in 25% cases in group A and 21.4% in group B, and very good' in 35.7 vs 10.7%. At 12 weeks, overall efficacy was seen in 71.4% in group A and 39.3% in group B. The study's findings suggest that microneedling plus tacrolimus with narrow band UVB may be a more effective treatment for vitiligo. **Conclusion:** Microneedling, a technique using delicate needles to puncture the dermis, has been shown to promote collagen synthesis and enhance the absorption of tacrolimus, a drug used for immunosuppression, potentially aiding in vitiligo repigmentation, but further localized studies are needed.

Key words: Band UVB, Microneedling, Pigmentation, Tacrolimus, Vitiligo.

INTRODUCTION

Vitiligo is an autoimmune disorder in which there is localized depigmentation. It is due to progressive loss of melanocytes resulting in milky white well demarcated macules and patches. It is classified in different types on the basis of distribution of depigmentation on body mainly into segmental and non-segmental Vitiligo. It is further classifies as stable and unstable Vitiligo. Stable Vitiligo is a type of Vitiligo in which no new lesion is formed in 3 months.[1]

The incidence of vitiligo is highest between the ages of 10 and 30 years, and it affects both sexes equally. Although several potential causes have been hypothesized for vitiligo, such as genetics, autoimmune mechanisms, psychological factors, metabolic variables, oxidative stress, and viral infections, the true origin of this skin condition is still unknown.[2,3]

Vitiligo is stressful and treatment is quite unsatisfying. Although steroids, topical calcipotriol, PUVA, with multivitamins are all recommended for vitiligo[4], none of these treatments are a definitive cure. Calcineurin inhibitors are another therapy option that have been shown to have fewer side effects than steroids and to be better suitable for long-term use, especially in sensitive areas. These treatment options can be given both as monotherapy and in combination. Clinical improvement depends upon type of Vitiligo and available treatment options.[5]

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Article received on: 12/12/2023
Accepted for publication: 19/04/2024

Skin microneedling was initially proposed for transdermal drug delivery. But it can cause epidermal changes which induce migration of melanocytes as well. Therefore microneedling can have dual effects on Vitiligo. Tacrolimus is a topical immunomodulator and inhibits calcineurin.[6] In a study, the repigmentation of >75% was observed in 50% of the patients when combined treatment given.[7,8]

As no local data is available regarding this topic, purpose of this study is to determine the added efficacy of microneedling with tacrolimus in the treatment of stable vitiligo in comparison with tacrolimus alone. Overall, both the techniques are effective in treating vitiligo, but the one with better outcome and lower incidence of adverse effects, will be recommended as routine practice. This study will strengthen the level of evidence for usage of this strategy. The results will be helpful for young physicians while managing these cases. Decision about which medication to use should be made by a healthcare professional who has considered all relevant factors and has evaluated the individual case.

METHODS

This RCT was conducted at the department of Dermatology, Madinah teaching hospital, Faisalabad for six (6) months after ethical approval from ethical review committee (Tuf/IRB/186/23) (5.6.23) of The University of Faisalabad, from 05-06-2023 to 5-12-23.

The aim of this randomized controlled trial was to compare the efficacy of microneedling plus Tacrolimus with narrow band UVB versus tacrolimus with narrow band UVB in the treatment of vitiligo. Vitiligo was defined as any patient with a medical condition in which white patches develop on the skin due to the loss of melanocytes. Further it can be categories as: Stable Vitiligo: Type of Vitiligo in which no new lesion form in last 3 months. Microneedling was defined as Cosmetic procedure in which skin is punctured with multiple tiny needles present in automated derma pen for transdermal drug delivery. Phototherapy was defined as treatment of diseases with Narrow-band (UVB 311-312nm).

All patients with Vitiligo who presented in Dermatology department were screened. All those with co-morbid conditions like diabetes and hypertension, or presence of any other autoimmune or inflammatory condition on the skin or any active infection were excluded. Pregnant or lactating females and those with keloidal tendency or in phase of active koebner phenomena were also not included in the study. Patients with unstable Vitiligo were excluded. After applying the inclusion and exclusion criteria, patients of both genders with stable Vitiligo for last 3 months were enrolled, with most of the lesions on the face. All of these were of the age, 15 to 60 years. 6 patients lost the follow up so excluded from the study. Total 28 patients who fulfilled the criteria and completed the treatment and presented to OPD for follow up were included in this study after signing informed consent.

Among the patients enrolled, two similar lesions were selected on face and each lesion was labeled as separate entity. Lesions were assigned as group A and B by using lottery method to randomize allocation of treatment. All lesions in group A were treated with microneedling plus topical tacrolimus 0.1% with narrow band UVB and those in group B with topical tacrolimus 0.1% and narrow band UVB. Micro needling was done after every 3 weeks in lesions of group X and tacrolimus ointment was applied twice a day in group both groups. Patients were followed up for 12 weeks after completion of treatment. Narrow band UVB was given twice a week. Since microneedling is an invasive procedure so patient cannot be blinded.

The study focused on gauging the effectiveness of microneedling sessions by evaluating the repigmentation response during subsequent follow-up visits. To achieve this, photographs of the patients' skin lesions were systematically captured at three crucial time points: baseline, 1 month after the final microneedling session, and 3 months post the last session. To ensure unbiased evaluation, a Professor from the Dermatology department meticulously examined the photographs without prior knowledge of the

specific treatment administered to the lesions. The assessment of repigmentation was conducted utilizing a comprehensive four-grade scale (G0-G4). The scale delineated varying degrees of repigmentation: G4 denoting excellence (≥75% repigmentation), G3 indicating very good results (50%-75% repigmentation), G2 signifying a good response (25%-50% repigmentation), G1 representing satisfactory outcomes (<25% repigmentation), and G0 reflecting poor results with no observable repigmentation. This meticulous approach allowed for a detailed and nuanced understanding of the treatment's impact on repigmentation, providing valuable insights into the effectiveness of microneedling in addressing skin lesions over the specified follow-up period. Successful repigmentation: Any patient whose skin showed more than 50% repigmentation was categorized as having successful pigmentation.

Analysis was done using SPSS 26. Mean and standard deviation was calculated for quantitative variables like age and frequency and percentage was calculated for qualitative variables. The outcome of the study was accessed by comparing the outcome in the abovementioned categories. Data of the outcome variable was stratified for age, gender, and post stratification chi square will be applied. P value < 0.05 was considered as statistically significant.

RESULTS

In this RCT we compared the efficacy of microneedling plus tacrolimus with narrow band UVB versus tacrolimus with narrow band UVB in the treatment of vitiligo. All patients had lesions on the face. After the approval, subjects were enrolled in the study after informed consent. A total of 34 patients were enrolled as per the inclusion criteria mentioned above. 6 patients lost the follow up so excluded from the study. Since it was a split face study so, Male and females were equal in both the groups. No gender bias was present. Study included 16 males and 12 females. Mean age of the patients was 29.4 + 11 years (min 15 and max 58).

After completion of treatment session, first Follow up visit (after 4 weeks) showed that outcome of the treatment was significant improvement in 17 of 28 patients (60.7%) in the group A (microneedling pus Tacrolimus with narrow band UVB) while outcome in group B (Tacrolimus with narrow band UVB) was 32.1% (9 of 28 patients showed significant improvement, p value of 0.03, statistically significant). Categorizing the efficacy or improvement into five levels as mentioned in the methodology showed that 'excellent' results were seen in 25% cases in group A and 21.4% cases in group B and 'very good' in 35.7 vs 10.7%. Details of efficacy 4 weeks after completion of session is shown in the Table-I. Similarly at 12 weeks of follow up after completion of sessions, overall efficacy was seen in 71.4% in group A and 39.3% in the group B, details of the follow up visit after 12 weeks is shown in the Table-II.

Groups	A		B		
Efficacy at 4 weeks after completion of session	**No.**	**%**	**No.**	**%**	**Total**
Yes	17.0	60.7	9.0	32.1	26.0
No	11.0	39.3	19.0	67.9	30.0
Total	28.0		28.0		56.0
p value = 0.03					

Table-I. Showing the details of efficacy after 4 weeks

Groups	A		B		
Levels of Out-come 4 weeks after completion of sessions	**No.**	**%**	**No.**	**%**	**Total**
Excellent	7.0	25.0	6.0	21.4	13.0
V. Good	10.0	35.7	3.0	10.7	13.0
Good	5.0	17.9	10.0	35.7	15.0
Satisfactory	3.0	10.7	4.0	14.3	7.0
No Change	3.0	10.7	5.0	17.9	8.0
Total	28.0	100.0	28.0	100.0	56.0

Table-II. Showing the details of efficacy after 12 weeks

Efficacy at 4 weeks follow up	No.	%	No.	%	Total
Yes	20	71.4	11	39.3	31
No	8	28.6	17	60.7	25
Total	28		28		56
p value = 0.03					

Groups	A		B		Total
Levels of Outcome 12 weeks	No.	%	No.	%	
Excellent	11.0	39.3	6.0	21.4	17.0
V. Good	9.0	32.0	5.0	17.9	14.0
Good	4.0	14.3	9.0	32.1	13.0
Satisfactory	2.0	7.0	3.0	10.7	5.0
No Change	2.0	7.0	5.0	17.9	7.0
Total	28.0	100	28.0	100.0	56.0

DISCUSSION

Vitiligo is a common pigmentary disorder that affects approximately one percent of the overall population. There is a wide variety of medical and surgical options for treatment. The use of microneedling as a treatment method for an increasing number of dermatological conditions is becoming increasingly common. It is also used to enhance the delivery of drugs transdermally through pores that have been created in the stratum corneum.[9]

This study compared the efficacy of microneedling plus tacrolimus with narrow band UVB versus tacrolimus with narrow band UVB in treating vitiligo. The study involved 34 patients with face lesions. Six patients lost follow-up and were excluded. The study included 16 males and 12 females, with a mean age of 29.4 + 11 years. After the treatment, the first follow-up visit showed significant improvement in 17 of 28 patients (60.7%) in group A (microneedling pus Tacrolimus with narrow band UVB) compared to 32.1% in group B (Tacrolimus with narrow band UVB). The efficacy was categorized into five levels: 'excellent' in 25% cases in group A and 21.4% in group B, and very good' in 35.7 vs 10.7%. At 12 weeks, overall efficacy was seen in 71.4% in group A and 39.3% in group B. The study's findings suggest that microneedling plus tacrolimus with narrow band UVB may be a more effective treatment for vitiligo.

In a research, there were a total of 403 lesions spread throughout 110 patients. During the course of treatment, more than 70 percent of the lesions exhibited some degree of varied repigmentation. Clinical response, defined as repigmentation of more than 50%, was shown in 42.0% of the lesions, but our study found that 60.7% of them did. Response was entirely determined by the location of the lesion, with facial lesions eliciting the most responses (73%), limbs (68%) and the trunk (53.5%). The treatment was favorably received by the patient. The preliminary data suggested that the combination of topical tacrolimus with NB-UVB phototherapy can potentially provide an alternative very effective method to the treatment of refractory vitiligo that is situated on the face, trunk, and limbs. It is necessary to collect data on the drug's long-term safety as well as conduct randomized controlled studies on a significant number of patients.[10]

In a study Ibrahim ZA, et al compared the effectiveness of treating vitiligo with microneedling combined with tacrolimus to that of treating the condition with calcipotriol and betamethasone. A total of twenty-five patients suffering from vitiligo were chosen to have microneedling and topical tacrolimus applied to their symmetrical patches. A response rate of approximately 32 percent was excellent. They came to the conclusion that the combination of microneedling with calcipotriol and betamethasone was more successful in treating the condition than its combination with tacrolimus. Both of these approaches are successful in overcoming resistant sites. Both approaches are risk-free, relatively inexpensive, and well-tolerated in the workplace, with few adverse effects.[11]

Miconeedling improves drug delivery through the skin. Ebrahim HM, et al. compared tacrolimus 0.1% ointment and microneedling for vitiligo treatment's efficacy and safety. One side of trial patients were given tacrolimus daily and other side underwent topical tacrolimus microneedling every two weeks. Excellent Repigmentation was seen in 50% of group II patients after treatment, compared to 29.2% of group I patients ($p = .02$). Group II responded faster than group I ($p = .002$). Group II had greater leg and extremity improvement than group I ($p = 0.003$). Group II had significantly higher c-kit expression than group I ($p = .01$) according to immunohistochemistry and no serious side effects were reported. The findings

suggested that tacrolimus and microneedling for vitiligo may be most effective and a cheaper method of menagement.[7] Comparable results were seen in our study.

Another study done by Ebrahim HM, et. al. on ninety patients with vitiligo with: group I microneedling with tacrolimus, group II microneedling only, and both groups underwent treatment at two-week intervals for a total of twelve sessions; group III was instructed to apply tacrolimus ointment 0.1% only twice a day for the duration of the study. When compared with the other groups, the overall improvement in the combined group, which was 76.6 percent, was significantly higher. Repigmentation was excellent in 66.6% of patients in group I (comparable to that reported in our study, compared to only 33.3% of patients in the other two groups (P =0.03). In comparison to the other groups, the combined group showed a marked and statistically significant improvement in the extremities (P less than.001). It has been reported that there were fewer sessions carried out in the combined group (P .001) in comparison to the microneedling.[8]

CONCLUSION

The utilization of exceedingly delicate needles to induce minute punctures in the dermis has demonstrated efficacy in promoting collagen synthesis. Nevertheless, tacrolimus is employed for the purpose of immunosuppression. It has been observed that microneedling has the potential to enhance the absorption of tacrolimus, thereby potentially augmenting its immunosuppressive effects, which can be beneficial in the repigmentation of vitiligo. Based on our study findings, it has been determined that the intervention in question demonstrates potential benefits. However, it is crucial to conduct additional localized studies to thoroughly investigate any potential adverse effects before considering it as a routine recommendation for patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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2	Tanzeela Khalid	Review of paper.	
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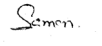
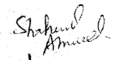
5	Saman Iqbal Goraya	Manuscript writing & Data collection.	
6	Shakeel Ahmad	Review of data & Discussion writing.	
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