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COMPARISON OF EFFICACY OF TCI MONOTHERAPY WITH TCI AND NARROW BAND UVB IN VITILIGO: A HOSPITAL BASED STUDY.

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Abstract

Background: *A skin condition known as vitiligo is an advanced depigmentation of the skin that is characterized by the development of depigmented macules that cause significant social and psychological distress. Although there are various therapy options available, vitiligo management is still a therapeutic challenge for many dermatologists. Topical calcineurin inhibitors, ultraviolet B phototherapy, and topical steroids are examples of conservative treatments.*

Objective: *This study aims to compare the effectiveness of tacrolimus monotherapy and narrowband ultraviolet B phototherapy (NB-UVB) for treating vitiligo.*

Materials and Methods: *For a period of two years, 100 vitiligo patients who presented to the dermatology outpatient department of the first Dali university associated hospital underwent a prospective and comparative study (from 2018-1-1 to 2019-12-31). All of the participants in this study met the inclusion and exclusion criteria after receiving the necessary ethical approval. According to the vitiligo data Proforma, demographic information was checked during the initial appointment.*
All individuals with vitiligo underwent a complete clinical and dermatological examination of their condition. The associated laboratory tests were all finished. It was assessed how much of the body's surface area is affected by vitiligo. On the basis of their course of therapy, patients were divided into two groups at random. Tacrolimus ointment was applied topically to 50 patients in group A twice daily. 50 patients in group B received topical medication three times per week in addition to NB-UVB phototherapy.
The VASI (Vitiligo Area Severity Index) was used to compare the effectiveness of the two groups from the beginning of the trial to its conclusion. Global ratings from both patients and physicians were calculated as part of the study's secondary efficacy measure. Software called SPSS 23.0 was used to do the statistical analysis. At p 0.05, the difference was statistically significant.

Results*: After 12 months of treatment, topical treatment alone outperformed Narrow Band UVB in terms of overall effectiveness. Patients treated with narrow band UVB plus topical treatment have earlier repigmentation response to lesions in the face, trunk, upper limbs, and lower limbs than those treated with topical treatment alone. When comparing the trunk, face, upper, and lower limbs for both types of therapies, lesions in the hands and feet require a lengthier course of treatment.*

Conclusion: *Narrow band UVB along with TCI is of higher efficacy, better tolerated and superior to TCI monotherapy in the treatment of vitiligo. There was a statistically significant reduction in percentage of VASI p= with Narrow Band UVB along with TCI group when compared to TCI mono therapy alone.*

Keyword: *vitiligo, topical Calcineurin inhibitor , Narrow band UVB, phototherapy*

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BACKGROUND:
A developing skin depigmentation condition with an unclear etiology, vitiligo is histologically thought to be caused by damage to effective melanocytes in the epidermis. It is one of the more common pigmentation disorders and includes a complex interplay of environmental and genetic factors that ultimately contribute to the destruction of melanocytes, resulting in the depigmented lesions [1].

Even though vitiligo has no significant impact on life expectancy, it is stigmatized by the community for sufferers due to a number of reasons, including misconceptions that it is the same as leprosy, taboos, unfamiliarity, and a lack of scientific research [2, 3].

This can be quite damaging and has been shown to result in significant indisposition, abridged self-esteem, a diminished quality of life, and a pitiful body image in vitiligo patients with significant psychiatric disorder. Due to their developing stages and readiness to form their own natural reasoning, children and adolescents are of particular importance [4].

Prevalence of vitiligo varies across populations. It is more common in Indian subcontinent (0.46%-1.13%) [5, 6] and lesser in Caucasians (0.38%) [7], African (0.34%) [8] and Chinese (0.093%) [9] Respectively. India has the highest rate of vitiligo tailed by Mexico and Japan [10].

On the basis of clinical presentation, various vitiligo variants are well-known. Vitiligo phenotypical expression is polymorphic. Vitiligo progresses in an unpredictably slow and difficult-to-control manner. But in other circumstances, it can remain for a long time in an unchanged state [11].

Most vitiligo cases are diagnosed clinically because of the typical appearance of the vitiligo lesions; however, in some cases, if the vitiligo lesions are not spread in design of conventional vitiligo, the misperception may arise with new hypomelanotic disorder, which can be helpful with inspecting wood lamp examination, biopsy, histopathology, and dermoscopy.

The problem will persist until we discover a remedy that provides a reliable and lasting solution through repigmentation. Topical medicines like Tacrolimus with potent topical corticosteroids, calcipotriol, pseudo catalase therapy, and phototherapies like Narrow Band Ultraviolet B (NB-UVB) and PUVA are a few examples of management techniques.
Tacrolimus, topical corticosteroids, and NBUVB together are also helpful for repigmentation that occurs quickly [12].

For the treatment of vitiligo, topical calcineurin inhibitors have two mechanisms of action: immunosuppression and melanocyte activation. In vitiligo, TCI prevents cytotoxic CD8+, an effector arm of autoimmunity. (By preventing calcineurin-intermediated phosphorylation of the nuclear factor of activated T cells).

By promoting melanocyte proliferation, migration, and melanin synthesis (increased MMP-2, MMP -9 activity, and increased endothelin B receptor appearance in melanoblasts), TCI promotes the repigmentation of vitiligo. It also supports the release of stem cell factors from keratinocytes after TCI treatment [13].

MATERIALS AND METHODS:
The main objective of this study is to assess and compare the efficacy and tolerability of topical TCI (topical calcineurin Inhibitor) with NB_UVB versus topical calcineurin Inhibitor (TCI) monotherapy in the dealing of vitiligo.
Study Design: This was a hospital based ‘prospective study’, patients those were diagnosed with vitiligo in Outpatient clinic of Dermatology department over a period of 2 years. Study was conducted at First affiliated hospital of Dali University. All patients those who satisfied the inclusion and exclusion criteria were involved in this study.
Sample Size: Total number of patients included in this study is 100, from the First Affiliated Hospital of Dali University since January 2018 to December 2019 out of which 48 were male and 52 were female. On the basis of treatment modalities, they were divided randomly into 2 groups. Group A comprised of 50 subjects (n=50) and Group B (n=50).
Inclusion Criteria: All patients whoever were diagnosed with vitiligo clinically, age group 15 to 75 year, Patients who have body surface area lesser than 20%, Patients having stable vitiligo and Patient who is ready to receive phototherapy.
Exclusion Criteria: Patients that are older than 75 years old and under 15 years old were not included. Also patients whose portion of the body's surface with vitiligo more than 20% . Individuals with severe systemic sickness, including hepatic, renal, and cutaneous diseases. who declined to give their permission individuals with a history of photosensitivity.

Screening procedures and Visits:
Each patient's initial appointment included a thorough clinical history. Name, age, sex, address, and OPD number were among the demographic characteristics that were recorded. A thorough case history was kept, including the date and time of the disease's beginning as well as its length, course, and progression. Together with solar exposure, triggering factors like mental stress and trauma were reported to be present or absent. Patients' employment histories, histories of photosensitivity, prior treatments, and family histories of vitiligo were also noted. Any related illnesses were noted,

including thyroid disorders, diabetes, anemia, and other autoimmune illnesses. The right lighting was used to evaluate each subject. The VASI was used to determine certain clinical parameters such as the total number and distribution of lesions, their sight and size, their location, and their percentage of body surface area involvement. The total length of the illness was reported. Koebner's phenomena, leukotrichia, perifollicular pigmentation, and systemic issues were all noted whether they existed or not. CBC, RBS, Blood Urea, Serum Creatinine, LFT, and TFT were among the blood and biochemical tests that were completed and reported.

Calculation of VASI Score (Vitiligo Area Scoring Index): The patient's body was divided into following six regions: upper extremities excluding hands and including axillary region, hands, trunk, lower extremities excluding feet and including buttocks with inguinal area, head and neck and feet. The palmar method was used to calculate the involvement of the vitiligo area for each body regions. One hand unit in palmar method includes the palm and volar surface of all the digits, which is 1% of total body surface area. For the elimination of the hands size variation in different persons one hand unit is defined to be volar hand which includes the finger of single investigator. A visual scale was used to evaluate the skin depigmentation pattern and then, each site was clinically evaluated. The residual depigmentation's extent was expressed as the following percentages: 0%, 10%, 25%, 50%, 75%, 90%, and 100%.

Depigmentation %	Affected area Description
100	No pigment is present
90	specks of pigment are present
75	depigmented area exceeds the pigmented area
50	the depigmented area and the pigmented area are equal
25	the pigmented areas exceed the depigmented area.
10	only specks of depigmentation

The total body VASI was calculated using the formula given below:
VASI= ∑ All Body sites [HAND UNITS] X [RESIDUAL PIGMENTATION] [14].

During the initial appointment and the monthly follow-ups, photos were taken. A major efficacy indicator known as VASI, which is the percentage change in depigmentation from the first visit to the end of the research period, was determined by direct clinical examination. Patient global improvement assessment, which was graded on a four-point scale, is a secondary efficacy indicator. Based on how the patients responded to the treatment, this was assessed. 1. Significantly improved. 2. A little bit better. 3. Same. 4. Worse

Result:
100 of the 102 patients who were enrolled in the trial finished it. Each group had one patient who dropped out of the research, so they were not included in the analysis.

In this study the basic demographic data indicates the broad comparison for age. Sharing of patients managed with topical treatment alone and topical treatment with NB-UVB. --Age in both groups were between the ranges of 15-65 years. The age group i.e. 26-45 year's population with mean ± Standard Deviation (39.06 ± 16.79).

Considering the gender distribution of patients, out of 50 patients treated with topical treatment, 23 were males and 27 were females. In 50 patients treated with topical treatment along with NB-UVB, 25 were males and 25 were females (no significant statistical difference between the groups, p= 0.689)

Regarding the most common precipitating factor for vitiligo is the family history. Out of 50 patients in Group A, 17 had positive family history, 6 had history of trauma, and 27 had no any associated precipitating factors. In Group B, 15 had positive family history, 8 had history of trauma, and 27 had no any associated precipitating factors

Considering the distribution of Vitiligo: Out of 50 patients in Group A, 20 were focal, 20 were segmental, 6 were vitiligo vulgaris, 2 were acro-facial and 2 were mucosal types of vitiligo. In Group B, 22 were focal, 18 were segmental, 4 were vitiligo vulgaris, 4 were acro-facial and 2 were mucosal types of vitiligo describes treatment Group A is treated with TCI. Group B is treated with TCI + NB UVB light.

In each group, the trunk, lower limb, and upper limb had the highest percentage distribution of lesion area. **Table 1, 2 & 3** Shows the mean VASI reduction and percentage reduction value of the VASI Score before starting the treatment of TCI monotherapy group (Gr A) was 2.39 and TCI with NB-UVB (Gr B) was 2.09. Mean VASI Score after treatment at the end of 12 months in Group A was 1.86 and of Group B was 0.974. The reduction in mean VASI Score was 53.57 % in Group B than Group A (23.27%) at the end of treatment (T =11.1 p = 0.0001)

In Table 4: Secondary efficiency parameters like 'Physician global assessment' and 'Patient's global assessment' speaks in favor of the cohort of TCI and NB UVB. In TCI cohort alone, 4% were satisfied with much better remission, 88 % percent reported that there was slightly better improvement and 8% reported that their lesion remain the same.

On the other hand, in TCI with UVB cohort 26 (52 %) patients were satisfied with Much better remission of lesion at the end of 12 months., 24 reported that they were slightly better from the beginning of the treatment. but none of each group reported about worsening of the lesion after 12 months on treatment. In Group B (TCI & NB UVB) superb repigmentation (76-100%) was documented in 8 patients in comparison to Group A (TCI monotherapy) where no patients recorded good repigmentation,

Table 1. Comparison of Mean VASI reduction in Group A and Group B

Duration	**Group A**		**Group B**		**Independent t-test**
	Mean	**SD**	**Mean**	**SD**	
Before Treatment	2.39	±1.303606	2.09	±1.131822	t= 13.405, p= 0.0001
After Treatment	1.86	±1.065172	0.974	±0.706547	t= 11.127, p= 0.0001

Table 2: Comparison of mean VASI Reduction between two Groups
Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Differences	Group A	50	.5300	.27958	.03954
	Group B	50	1.1160	.70923	.10030

Table 3: Comparison of Percentage of Reduction in mean VASI between two Groups
Paired Samples Statistics

	Mean		N	Std. Deviation	Std. Error Mean
Pair 1	VASI Reduction % Group-A	23.5770	50	13.83495	1.95656
	VASI Reduction % Group- B	53.5794	50	20.04701	2.83507

Table 4: Patient's Global assessment score

Score	**Comment**	**No. of Patients**	**Group A (N)**	**Gr A (%)**	**Group B (N)**	**Group B (%)**	**Total (%)**
1	Much Better	28	2	4	26	52	28%
2	Slightly better	68	44	8	24	48	68%
3	Same	4	4	8	0	0	4 %
4	Worse	0	0	0	0	0	0%
Total		**100**	**50**		**50**		**100**

Table 5: Side effects of different treatments received by Group A and Group B of vitiligo patients.

Side Effects	**Gr A(N)**	**GrA(%)**	**Gr B (N)**	**Gr B (%)**	**Total**	**%**
Erythema	0	0	7	14	7	7%
Pruritus	0	0	2	4	2	2%
Atrophy	2	4	0	0	2	4%
Burning	5	10	0	0	5	10%
None	43	86	41	82		4%
Total	**50**		**50**			**100%**

Discussion:

White patches of skin are a symptom of the acquired condition vitiligo, which affects pigmentation. Calcineurin Inhibitors can be used as a monotherapy for vitiligo due to their immunomodulatory effects. Despite this, TCI monotherapy only has a little amount of success in curing vitiligo. Narrow-band UVB phototherapy can replace vitiligo lesions (NB-UVB). In this study, the management of vitiligo is examined between TCI monotherapy and TCI plus NB-UVB combination therapy.

The goal of the current study was to assess this form of treatment that may be beneficial for vitiligo sufferers. In this clinical judgment trial, patients with vitiligo (BSA less than 20% involvement) are compared for efficacy between TCI (0.03% Tacrolimus) and TCI plus NB-UVB. The goal of this study was to determine whether using TCI topical calcineurin inhibitor only once would be preferable to adding NB UV B.

According to the data presented and data from the literature, NB UVB phototherapy with topical calcineurin inhibitor was a safe strategy for treating people with vitiligo with no clinically significant adverse effects. Many treatment approaches, such as topical prednisolone, topical calcineurin inhibitors, and NB UVB, are used to treat vitiligo either separately or in combination [15].

In thirty vitiligo patients, Behrooz et al. (2017) compared the efficacy of pimecrolimus cream monotherapy to pimecrolimus cream plus NB-UVB. According to the study, combined therapy significantly increased repigmentation compared to monotherapy (74.1% vs. 42.8%, p0.05) [16].

These results are incorporated with our study results which revealed VASI reduction in group B (combined therapy) by 53% and 23% in group A (monotherapy) with significant differences between groups.

Moreover, Liu et al meta-analysis of seven randomized controlled trials from 2019 found that TCI with NB-UVB combination therapy is more effective than TCI mono-therapy at re-pigmenting vitiligo lesions. According to the meta-analysis, the blend therapy group significantly outperformed the monotherapy group in terms of overall response rate (OR 2.94, 95% CI 2.09-4.14, p0.001) and size reduction of vitiligo lesions (weighted mean difference -3.15, 95% CI -4.31 to -1.99, p0.001).

In accordance with the findings of this study, TCI monotherapy group (A) VASI reduction and percentage reduction significant was 2.39, and TCI plus NB-UVB group (B) was 2.09. At the end of a year of treatment, Group A's mean VASI Score was 1.86, whereas Group B's was 0.974. At the end of treatment, Group B experienced a mean VASI Score decline that was 53.57% greater than that of Group A (23.27%) (T =11.1, p = 0.0001) [17].

Ilona Hartmann endorsed the idea that combined therapy is more effective than monotherapy in patients with large zones of lesions [18].

Njoo et al. (2000) conducted a study with 51 volunteers between the ages of 4 and 16 and used 311 nm NB UVB phototherapy as a generalized treatment for vitiligo. In 53 percent of his patients, repigmentation of vitiligo lesions was claimed to have been achieved [19].

After receiving NB- UVB treatment for a year, Kanwar et al. reported complete repigmentation in 71.4% of their participants and mid-modest repigmentation in 14.3% of the patients. (20)

In 80% of their 10 pediatric volunteers, Brazelli et al. attested that phototherapy produced a satisfactory response [21].
Selma Baker et al. documented a number of examples in which the severity of the condition was inversely correlated with therapy response. She said that in participants with an average disease duration of 15 months, complete repigmentation was achieved. Just mild to moderate repigmentation was reported by subjects with 96 months of illness. The face and neck experienced improved treatment response, whereas the hands, feet, knees, and elbows—where there are acral and bone projections—showed minimal improvement [22].

D Fai et al studied combined treatment between NB- UVB and combined with TCI over 110 patients and found depigmentation more than 50 percent was observed in 42 % of lesions. We can consider our results in agreement with them as group B in our study showed improvement 53 % in VASI reduction which means combined treatment was effective more than single TCI treatment [23]

Giuseppe Stinco et al. highlighted how the response to therapy varied depending on the anatomical placement of the lesions without statistically significant difference in repigmentation, with the most significant outcomes being reached for lesions of the face with TCI and of the open neck with NB UVB. NB - UVB phototherapy may be the most effective treatment for global vitiligo, while topical immunomodulators are the best option for vitiligo that is localized [24].

Repigmentation of the facial lesion was higher in patients treated with combination TCI and NB- UVB compared to placebo (64.3 vs. 25.1%), according to Iraj et al. That backed up our investigation, where we reduced by 53.1% [25].

Afseen Bilal et al. provided a comparison of the efficacy between two groups, one of which received tropical tacrolimus and NB-UVB treatment and the other of which received simply NB UVB treatment. Their findings indicated that the effectiveness was 30% with monotherapy and 53.5% with pooled treatment. They demonstrated that combination therapy out-performs monotherapy[26].

Conclusion:
The evidence currently available suggests that TCI and NB-UVB combination therapy is more effective than TCI monotherapy at re-pigmenting vitiligo lesions. When compared to monotherapy, the combination form of treatment yields better results.

Our comparison study's findings demonstrated that using (Tacrolimus 0.03%) in combination with NB UVB is safer for the treatment of vitiligo. Patients with vitiligo who are not responding to TCI alone may be considered candidates for combination therapy. To determine the ideal combination therapy regimen, treatment duration, and long-term safety of this strategy, additional research is required.

Abbreviations: TCI : topical Calcineurin Inhibitor , NB UVB : Narrowband ultraviolet B, VASI : Vitiligo Area Scoring Index
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Authors contribution: 1 has conducted cases studies and documented the data from the study population. 2 gave significant and important contribution in revising the text and 3 significantly contributed to revise the article.

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