

Original Research Article

308 nm Excimer laser combined with 0.1% tacrolimus ointment for treatment of localized vitiligo

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ABSTRACT

Background: Vitiligo is a long-term skin disease identified by spots of the skin missing their pigment. The spots of skin changed turn white and usually have distinctive perimeters. The hairs that exist on the skin may also turn white due to this disease. Patients inside of the mouth and nose may also be affected by vitiligo. The objective of the study was to analyze results of using 308 nm excimer laser combined with tacrolimus 0.1% ointment for treating the patients associated with localized vitiligo.

Methods: This research adopted a mixed method consisting a qualitative approach, a survey of related articles from renowned journals. Regarding data collected from patient's database who underwent treatment at BSMMU, Bangladesh. Patients are divided into 3 groups. The first group included 30 vitiligo patients treated with topical 0.1% tacrolimus ointment applied twice daily for 10 weeks of follow-up. The second group consists of 30 vitiligo patients treated with 308 nm excimer laser applied three times a week for 10 weeks of follow-up. The third group of 30 vitiligo patients treated with 308 nm excimer laser combined tacrolimus 0.1% ointment applied twice daily for tacrolimus and three time a week for 308 nm excimer laser for 10 weeks).

Results: The research result showed that the combined treatment of 308 nm excimer laser with 0.1% tacrolimus ointment and 308 nm excimer laser monotherapy are effective, reliable and well tolerated for the vitiligo treatment.

Conclusions: The research result confirms the efficacy of excimer laser therapy in vitiligo patients, suggesting that an association with 0.1% tacrolimus may represent an advance in the treatment of the disease.

Keywords: Vitiligo, Lasers, Excimer, Skin, Tacrolimus

INTRODUCTION

Vitiligo is a chronic, idiopathic inherited disorder, which is identified by increasing loss melanocytes from the epidermis and the epidermal appendages. Vitiligo is also said to be a long-term skin disease identified by spots of the skin falling their pigment.¹

Whitton et al also added that, the spots of skin affected turn white and normally have sharp margins.¹ The hair from the skin may also turn white in color. The inside of the mouth and nostrils may also be included.² Typically, both surfaces of the body are affected.¹ Usually, the spots found

on regions of skin that are revealed to the sun. It is also notable in patients with dark skin.²

Vitiligo may cause psychological stress and those affected may be stigmatized.¹ Nevertheless, prosperous therapy of vitiligo in all patients is still a phantasm, although different combination modelities like topical steroids, immunomodulatory, phototherapy and surgical therapies are commonly used.

This dermatosis may cause psychological disorders, even causing the damage of one's social status in some societies. Patients often lack relevant scientific knowledge

and emotional comfort; the clinical response, adherence to the treatment, and even resilience in face of potential therapeutic failures depend on a good physician-patient bond.

Considering the wide variety of medical treatments currently possible, dermatologists must assess their patients in a holistic way.^{3,4}



FIGURE
Vitiligo. Sharply demarcated depigmented patches can be seen.

Objective

The objective of this study was to evaluate and compare the clinical efficacy and side effects of 0.1% tacrolimus topical ointment, 308 nm excimer laser monotherapy, and combination therapy of 0.1% tacrolimus topical ointment and 308 nm excimer laser in treating vitiligo patients to find out a better treatment method.

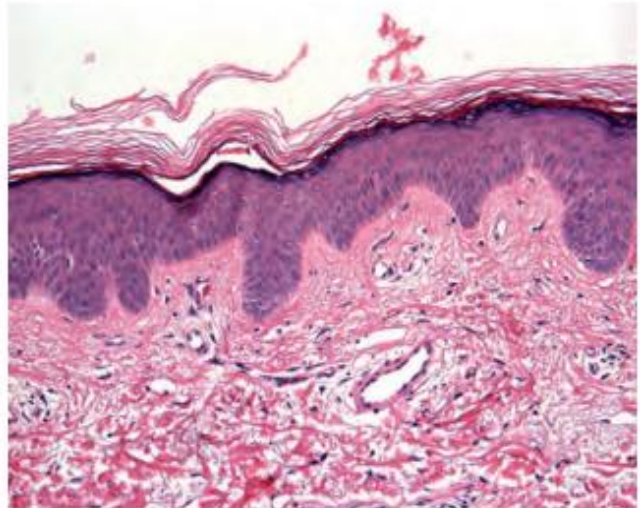


FIGURE
Vitiligo. There is complete absence of both melanocytes and melanin.

Figure 1: Vitiligo patches on patient and vitiligo microscopic view.⁵

METHODS

Current study was a retrospective study, randomized clinical trial. All patients taking treatment for localized vitiligo in the department of dermatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

From August 2017 till August 2019 were included in the study. In total 90 patient data was collected. The patients were in good general health with no evidence of any major systemic disease. Sample size for current study was calculated using the formula:

$$VASI = \sum_{(\text{all body size})} (\text{hand units}) \times (\text{depigmentation})$$

VASI was determined as the product of vitiligo caused area where each hands unites measured at 1% per unit which has possible values of 0, 10, 25, 50, 75, 90, 100%. VASI is generally applied to the whole body using the VASI formula where possible range is (0-100).

Inclusion criteria

Inclusion criteria for current study were: all clinically diagnose cased of vitiligo. Also, regular follow-up data of those patient who came to regular follow-up for 10 weeks.

Exclusion criteria

Exclusion criteria for current study were: patient who took another therapy with topical 0.1% tacrolimus ointment for treatment of vitiligo. Also, patient who took other drugs with 308 nm excimer laser for combined therapy for vitiligo.

Procedure

This was a two years retrospective study of data collected from August 2017 to August 2019 in department of dermatology of Bangabandhu Sheikh Mujib Medical University. It involved the patients who were treated by 0.1% tacrolimus ointment topically, who were treated with combined therapy of 308 nm excimer laser and 0.1% tacrolimus ointment topical, and who were treated with 308 nm excimer laser monotherapy.

Patient were divided by three groups. Group A included the patients treated with topical 0.1% tacrolimus ointment, group B included the patients treated with 308 nm excimer laser monotherapy and group C included the patients treated with the combined therapy of topical 0.1% tacrolimus ointment and 308 mn excimer laser. Obtained data of those patients who fulfill the inclusion criteria was enter on Microsoft excel spreadsheet and analysis was done using SPSS 22.0 software. The result was published

after the data analysis. Patient's personal information has been kept confidential. The ethical committee of Bangabandhu Sheikh Mujib Medical University approved study.

RESULTS

Among 90 patients, we performed a comparative quantitative analysis in three (three) groups (A, B, C) of patients associate with vitiligo. There were two statistical analysis done by SPSS software to come up with the conclusion, which treatment model is more effective to treat vitiligo-affected patients.

In first test we had seen that the mean value for treatment model A, B, and C is 6.66, 5.35 and 2.74 which means the average data value of treatment model C was less than other two treatment model. Therefore, the VASI of treatment model C (combined treatment of 308 nm excimer with 0.1% tacrolimus) were lesser than the rest of the two treatments model.

We saw the estimated marginal means shows that the adjusted means of treatment model A, B and C are 6.654, 5.349 and 2.758 which means the treatment model C (combined treatment of 308 nm excimer with 0.1% tacrolimus ointment) had the lowest adjusted mean of 2.758. That means the data values of treatment model C were lesser than the data values of treatment model A and B. Age was not a continuous variable. As per the result, the prominent age group for the vitiligo patients are from age 30 to age 34 years. The most prominent age for the vitiligo patients was 32 years. This age group was encompassing 43.33 percent of the vitiligo patients. Then the age group 25 to 29 years. Both of these age groups are encompassing 33.33 percent of the vitiligo patients. Age group 20 to 24 years and 35 to 39 years encompassing the lowest percentage of vitiligo patients which is 11.11 and 12.22 percent.

We saw from the Table 2, the treatment model A (using 308 nm excimer laser), B (using 0.1% tacrolimus) and C (using 308 nm excimer combined with 0.1% tacrolimus) was normally distributed. If the significant value of the Shapiro-Wilk test was greater than 0.05, then the data was normal. If it was below 0.05, the data was significantly deviate from normal distribution. From the above Table 3,

we can observe that, in treatment model the difference of mean for mVASI before Rx-mVASI after Rx was 5.09, for treatment model B was 6.40 and for treatment model C, which was the combined treatment of 3.8 nm excimer laser and 0.1% tacrolimus ointment, the difference of mean, was 8.94. We saw, all of these 3 treatments procedure was effective, but the most effective is the combined treatment of 3.8 nm excimer laser and 0.1% tacrolimus ointment. We saw the mean difference was highest in treatment model C, that means combined treatment lessen the vitiligo effected area or mVASI after Rx more than the other 2 treatments model. From the Table 4 of tests of between subject's effects shows, the treatment model has a significance level of 0.000, which was less than 0.05. Which indicates that it had a significant effect on mVASI after Rx. We can further look to the parameter estimation to determine the size of the effect.

From the Table 5 of estimated marginal means, the output shows that the adjusted means (controlling for the covariate 'mVASI before Rx') for each treatment model group. This simply means that the effect of 'mVASI before Rx' had been statistically removed. From these adjusted means, it was clear that treatment A has the higher mVASI after Rx after treatment. Table 5 also shows that treatment model C (308 nm excimer combined with 0.1% tacrolimus treatment) has the lowest adjusted means meaning treatment model C has lower mVASI after Rx. From the Table 6, descriptive statistics of Wilcoxon Signed-rank test two-related sample non-parametric tests, we can see that the mean value is lower in mVASI after Rx, which is 4.92 than the mVASI before Rx, which is 11.73. As the after treatment mean value is lower, the result is satisfactory.

From the Table 7 Wilcoxon signed rank test, we observed that there were no positive ranks. Which means there was no value of mVASI after Rx, which was greater than mVASI before Rx. The Table 7 also shows that there are 90 negative ranks. Which means all the data value of mVASI after Rx were smaller than all the data value of mVASI before Rx. Now, from the Table 8 test statistics of Wilcoxon signed ranks test, we can see that the Z value was -8.239. In addition, the significance level is 0.00, which was lower than 0.05, which was significant. Therefore, the results showed that the severity of vitiligo was lower after the treatment, which means the treatment was successful.

Table 1: Demographic data of patients.

Age (years)	Gender		Total
	Male	Female	
Less than 20	0	0	0
20-24	2	8	10
25-29	5	25	30
30-34	8	31	39
35 and above	2	9	11
Total	17	73	90

Table 2: Tests of normality.

Treatment model	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistics	df	Sig.	Statistics	df	Sig.
mVASI after Rx A	0.074	30	0.200	0.978	30	0.776
mVASI after Rx B	0.141	30	0.133	0.954	30	0.215
mVASI after Rx C	0.187	30	0.009	0.947	30	0.144

Table 3: Difference of Mean (mVASI before Rx-mVASI after Rx).

Treatment model	Mean (mVASI before Rx)	Mean (Rx-mVASI after Rx)	Difference between mVASI before Rx and Rx-mVASI after Rx
A	11.76	6.67	5.09
B	11.75	5.35	6.40
C	11.69	2.75	8.94

Table 4: Tests of between-subjects effects dependent variable: mVASI after Rx.

Sources	Type III sum of squares	df	Mean square	F	Sig.	Partial Eta squared
Corrected model	264.121	3				
Intercept	9.082	1	88.040			
mVASI before Rx	25.714	1	9.082	22.200	0.000	0.436
Treatment model	235.909	2	25.714	2.290	0.134	0.026
Error	341.056	86	117.954	6.484	0.013	0.070
Total	2784.107	90	3.966	29.743	0.000	0.409
Corrected total	605.177	89				

Note: R squared = 0.436 (Adjusted R squared=0.417).

Figure 5: Treatment model dependent variable: mVASI after Rx.

Treatment model	Mean	std. error	95% confidence interval	
			Lower bound	Upper bound
A	6.654 ^a	0.364	5.932	7.337
B	5.349 ^a	0.364	4.626	6.071
C	2.758 ^a	0.364	6.071	3.481

Note: ^aCovariates appearing in the model are evaluated in the following values: mVASI before Rx = 11.73109.

Figure 6: Descriptive statistics.

Variables	N	Mean	SD	Minimum	Maximum
mVASI before Rx	90	11.37	2.055	7.489	17.021
mVASI after Rx	90	4.920	2.608	0.6330	12.840

Figure 7: Ranks.

Variables		N	Mean rank	Sum of ranks
mVASI after Rx	Negative ranks	90 ^a		4095.00
mVASI before Rx	Positive ranks	0 ^b	45.50	0.00
	Ties	0 ^c	0.000	

Note: ^amVASI after Rx < mVASI before Rx; ^bmVASI after Rx > mVASI before Rx; ^cmVASI after Rx = mVASI before Rx.

Figure 8: Test statistics.

Tests	mVASI after Rx- mVASI before Rx
Z	-8.239 ^b
Asymp Sig (2-tailed) t	0.00

Note: ^aWilcoxon signed ranks test; ^bbased on positive ranks.

DISCUSSION

The analysis in the research was conducted to investigate the effect of 308 nm excimer laser treatment, individual 0.1% tacrolimus ointment treatment; and 308 nm excimer laser combined with 0.1% tacrolimus ointment treatment. A total number of 90 patient's data was recorded and analyzed. Overall, the combination group could promote the vitiligo patients' clinical outcomes without any additional side effect.⁶

We performed a comparative quantitative analysis in three groups of patients associate with vitiligo. The study included 90 patients, in which one group had 30 patients who had 308 nm excimer laser treatment to lessen their vitiligo. Other 30 patients had only 0.1% tacrolimus ointment treatment to lessen their vitiligo. In addition, the other 30 patients had combined treatment of 308-nm excimer laser and 0.1% tacrolimus ointment to lessen their vitiligo effected area. Required data were collected and analysis was done by SPSS software followed by which the results were compiled and discussed in the previous chapter. The treatment model A, B and C's VASI measurement before and after treatment were all well recorded.

There were two statistical analysis done by SPSS software to come up with the conclusion, which treatment model was more effective to treat vitiligo-affected patients. The first test was two-way independent ANOVA test. Where we had seen that the mean value for treatment model A, B, and C was 6.66, 5.35 and 2.74 which means the average data value of treatment model C is less than other two treatment model. Therefore, the VASI of treatment model C (combined treatment of 308 nm excimer with 0.1% tacrolimus) was lesser that the rest of the two treatments model.

Then the table of estimated marginal means shows that the adjusted means of treatment model A, B and C are 6.654, 5.349 and 2.758 which means the treatment model C (combined treatment of 308-nm excimer with 0.1% tacrolimus ointment) has the lowest adjusted mean of 2.758. That means the data values of treatment model C was lesser than the data values of treatment model A and B.

The second statistical analysis conducted on SPSS was the Wilcoxon sign test. It was a statistical comparison test works with ration data.⁷ As we wanted to test whether test the VASI of vitiligo affected area after treatment are getting lesser than the VASI of vitiligo affected area before treatment, we ran the Wilcoxon sign test. The test result showed that the mean value of mVASI after Rx was lower than the mean value of mVASI before Rx ($4.92 < 11.73$) meaning the result was satisfactory as the after-treatment value was lower than the before treatment value. In addition, from the ranks table we saw that there were 90 negative ranks, meaning all the differences of after treatment with after treatment (mVASI after Rx-mVASI

before Rx) was negative. Which again means all the VASI value was lesser after treatment. This test was also significant as the significance level was 0.00, which was less than 0.05.

CONCLUSION

Our results confirmed that the efficacy of 308 nm excimer laser therapy in vitiligo, suggesting that an association with 0.1% tacrolimus ointment may represent an advance in the treatment of the disease. Furthermore, this study suggests that, an association with 0.1% tacrolimus ointment could enhance the clinical response in vitiligo-affected area, especially in more resistant anatomical sites, without an increase in side effects. Indeed, the combination of 308 nm excimer laser with 0.1% tacrolimus ointment could enhance the clinical response interfering with immunological pathways of the patients involved in the pathogenesis of vitiligo. In addition, further researches and studies are required in order to identify therapeutic protocols and longtime safety profile of the disease. In addition, with different treatment options available for vitiligo, dermatologist should evaluate the patient holistically, especially when the disease vitiligo can have deep emotional impacts and influence on the quality of patient's life.

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