Original Article

Efficacy and Safety of Topical Timolol for the Treatment of Facial Angiofibroma in Children with Tuberous Sclerosis Complex

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ABSTRACT

Objective: This study aimed to assess the efficacy and safety of topical timolol in treating facial angiofibromas (FAs) in pediatric patients with tuberous sclerosis complex (TSC). **Methods:** A prospective clinical trial was conducted involving 15 children diagnosed with TSC and presenting with FAs. The participants were administered topical timolol gel 0.5% twice daily. Prior to the intervention, the severity of FAs in each patient was evaluated using the FA severity index (FASI), which assessed erythema, size, and extent of lesions. Clinical response was assessed at weeks 2 and 4 during the intervention period as well as 1 month after discontinuation of treatment. **Findings:** Four weeks after discontinuing topical timolol 0.5%, statistically significant reductions were observed in the mean FASI score, erythema, size, and extent of lesions ($P < 0.0001$, $P < 0.0001$, $P = 0.012$, $P = 0.008$, respectively). FASI scores at 4 and 12 weeks postintervention, as well as 4 weeks after treatment cessation, demonstrated a significant decrease compared to baseline ($P < 0.001$). Erythema and extension scores also exhibited a significant decrease 1 month after treatment cessation compared to baseline ($P < 0.05$), while the mean size of lesions before and after the intervention did not show a statistically significant difference ($P = 0.004$). **Conclusion:** Topical timolol 0.5% represents a cost-effective and readily available treatment option for pediatric patients with FAs associated with tuberous sclerosis.

Keywords: *Angiofibroma, topical Timolol, tuberous sclerosis complex/facial angiofibroma severity index*

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Introduction

Tuberous sclerosis complex (TSC) shows variable presentations, include multiple benign hamartomas in the brain, eyes, heart, lung, liver, and skin.[1,2] The

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most common skin lesions of TSC include angiofibroma, which is usually seen on the malar area of the face, hypopigmented macules, shagreen patch, which are typically seen on lumbosacral skin and forehead brown fibrotic plaques, which might be the first sign of TSC in infancy.[3,4]

Treatment of angiofibroma has been a challenging issue. On the one hand, there is no effective and standard treatment, and on the other hand, the proposed treatments that are used are associated with recurrence. Current treatment for facial angiofibroma (FA) includes pharmacological and nonpharmacological remedies. Nonpharmacological treatments include vascular laser, ablative laser, and tissue destruction procedures costly with unsatisfactory results.[5,6] One of the recommended drug treatments is topical rapamycin and timolol.[7-14]

Although different managements have been introduced for angiofibroma, there is no gold standard treatment, and despite these treatments, the relapse rate has been high, so finding an effective treatment with a lower rate of side effects is needed. In this study, the effect of topical timolol on FA and its effect on erythema, size, and extension of angiofibroma was evaluated.

Methods

This study designed as a before-after clinical study for the treatment of FA in children with TSC, referred to outpatient neurology or dermatology clinic of Imam Hossein Children Hospital affiliated Isfahan University of Medical Sciences, Isfahan, Iran. The selected patients had a definite diagnosis of TSC with two major or one major plus two minor features of TSC.[5,15,16] Parents of all cases filled the informed consent to enter the study. Patients with active skin infection, using drugs that interact with timolol, history of asthma, hypersensitivity to beta blocker, and other topical treatments in the last year for treatment of TSC, were excluded. Other exclusion criteria after the treatment consist of cutaneous or systemic reactions, skin infection, or refusal to continue the study. This study was approved by the ethical committee at Isfahan University of Medical Sciences with ethics ID IR.MUI.MED.REC.1398.589 and registered in the Iranian Registry of Clinical Trials (IRCT) with IRCT ID IRCT20171230038142N18. After explaining the procedure to patients and their parents and signing informed consent, history taking and physical examination were done then photographs of skin lesions were taken before treatment and in each follow-up visit.

For preparing 100 g of 0.5% Timolol gel, 85 mL of distilled water was heated to the boiling point temperature, then heat source was turned off and at 80°C, 180 mg Paraben and 20 mg Propylparaben were added to it. Then at 50°C, 1 g of carbomer 934 was added. About ½ h, when the carbomer hydrated, the solution was stirred by a glass rod for 10 min. When the temperature reached 25°C, 500 mg of timolol, which was dissolved in 10 ml of water, was added to the solution and was stirred for 10 min to make a uniform solution. If the PH of the formulation was acidic, triethanolamine was added to neutralize it. Finally, the formulation is packed in soft tubes.

Parents have been taught to use a thin layer of topical 0.5% timolol on patient's facial skin lesions twice a day (in the morning and in the evening). Patients are advised not to use other topical agents during the trial. Patients were visited 4 weeks and 12 weeks after the intervention, also 4 weeks after withdrawal treatment.

At baseline, FA in each patient was scored based on the FA severity index (FASI) in terms of three features: Erythema, size, and extent of lesions.[17-19] After the intervention, the patients were evaluated in 4 and 12 weeks of treatment and 4 weeks after stopping treatment. Patients are informed about possible side effects and were told to contact about complications. Side effects of topical timolol 0.5% such as erythema, itching, scaling and rarely dyspnea were noted.

Statistical indices of frequency, frequency percentage, mean, standard deviation, mean, and range were used to describe the data. The Friedman test is used to compare the mean FASI score in repeated measurements and the Wilcoxon test was used to compare the mean scores of FASI, erythema, size, and extension from baseline and 4 and 12 weeks after starting drug treatment and 4 weeks after stopping drug treatment. For comparison between groups, bonferroni correction was used for multiple tests, and in all comparisons, the statistical significance level of 5% was considered. Data were analyzed using a statistical significance level of 0.05 using the SPSS software version 20 (SPSS Inc., Chicago, IL, USA).

Results

Fifteen patients with TSC were included in the study. One of the patients was excluded from the study due to the drug complication of cutaneous erythema (missing percent = 6.6%). The mean age of patients was 9.09 ± 3.8 years and seven patients were girls (46.7%). Two children (13.3%) were unable to study and the average weight of these children was 29.83 ± 12.9 kg (median = 27.5 kg, range = 15–60 kg). Parents of 12 patients (80%) did not have a family history of marriage and ten patients (66.7%) had no family history of the disease.

Four weeks after withdrawal of topical timolol 0.5%, the mean FASI score, erythema, size, and extension of patients were statistically significantly reduced ($P < 0.0001$, $P < 0.0001$, $P = 0.012$, and $P = 0.008$, respectively). The comparison of FASI score, erythema, size, and extension results at different times is given in Table 1 and Figure 1.

In the *post hoc* study, the results obtained by comparing the time of baseline and 4 and 12 weeks after drug treatment (months 1 and 3), and 4 weeks after drug discontinuation (month 4), FASI score 4 and 12 weeks after intervention and 4 weeks after drug discontinuation significantly decreased compared to baseline ($P < 0.001$). Erythema and extension scores also showed a significant decrease compared to baseline 1 month after cessation of treatment, but the mean size before and after the intervention did not show a statistically significant difference. The results of a two-to-two comparison of FASI score, erythema, size, and extension in baseline and 4 and 12 weeks after the intervention and 4 weeks after withdrawal of drug treatment are given in Table 2.

Table 1: Comparison of facial angiofibroma severity index score, erythema, size and extension results at baseline, 4 weeks, 12 weeks after the start of treatment and 4 weeks after stopping of treatment (n=14)

Outcome	Mean±SD				P^+
	Baseline	Week 4	Month 3	Month 4	
Erythema	1.71±1.2	0.43±0.64	0.36±0.49	1.07±0.73	<0.0001
Size (mm)	1.64±0.74	1.14±0.36	1.07±0.47	1.14±0.36	0.004
Extension	2.43±0.51	2.29±0.46	2±0.55	2±0.55	0.002
FASI score	5.79±2	3.38±1.09	3.34±1.15	4.21±1.18	<0.0001

$^+$Friedman test. FASI=Facial angiofibroma severity index, SD=Standard deviation

The mean difference between erythema score, size, and extension and FASI score in the group with a history of seizures, 12 weeks after treatment compared to before starting treatment, was less than the group without a history of seizures, but this difference was not statistically significant. Except for the mean score of erythema, mean score, extension and FASI score 12 weeks after treatment compared to before starting treatment in the group with cephalic fibrosis plaque decreased more than the group without it, and this difference was not statistically significant. Details of the relationship between the difference in erythema score, size, extension and FASI, 12 weeks after treatment compared to before the start of treatment with a history of seizures, the presence of cephalic fibrosis plaque and the ability to study are given in Table 3.

Also, in the group with the ability to study compared to the opposite group, the mean score of erythema, size, extension and FASI score decreased, but this decrease was not statistically significant. There was no statistically

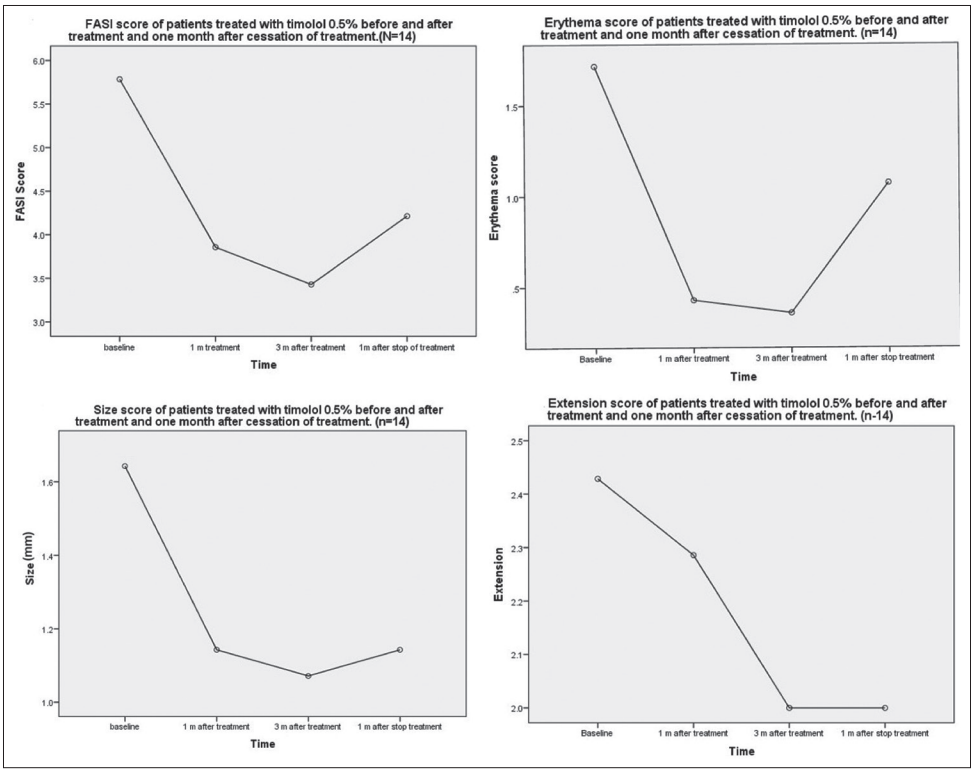

Figure 1: Comparison of FASI score, erythema, size, and extension results at different times. FASI = Facial Angiofibroma Severity Index

Table 2: The results of a two-to-two comparison of facial angiofibroma severity index score, erythema, size and extension in baseline and 4 and 12 weeks after the intervention and 4 weeks after withdrawal of drug treatment (*n*=14)

Outcome	Time	Mean difference score	*P*+	95% CI for difference	
				Lower bound	Upper bound
FASI score	1				
	2	1.92	0.001	0.73	3.12
	3	2.35	<0.0001	1.11	3.6
	4	1.57	0.002	0.55	2.58
	2				
	1	−1.92	<0.0001	−3.12	−0.73
	3	0.42	>0.05	−0.27	1.13
	4	−0.35	>0.05	−1.05	0.34
	3				
	1	−2.35	<0.0001	−3.6	−1.11
	2	−0.42	>0.05	−1.13	0.27
	4	−0.78	<0.0001	−1.13	−0.43
	4				
	1	−1.57	0.002	−2.58	−0.55
	2	0.35	>0.05	−0.34	1.05
	3	0.78	<0.0001	0.43	1.13
Erythema	1				
	2	1.28	<0.0001	0.6	1.97
	3	1.35	0.001	0.52	2.19
	4	0.64	0.04	0.02	1.26
	2				
	1	−1.28	<0.0001	−1.97	−0.6
	3	0.07	>0.05	−0.44	0.58
	4	−0.64	0.04	−1.26	−0.02
	3				
	1	−1.35	0.001	−2.19	−0.52
	2	−0.07	>0.05	−0.58	0.44
	4	−0.71	<0.0001	−1.10	−0.32
	4				
	1	−0.64	0.04	−1.26	−0.02
	2	0.64	0.04	0.02	1.26
	3	0.71	<0.0001	0.32	1.1
Size	1				
	2	0.5	>0.05	−0.04	1.04
	3	0.57	>0.05	−0.05	1.19
	4	0.5	>0.05	−0.13	1.13
	2				
	1	−0.5	>0.05	−1.04	0.04
	3	0.07	>0.05	−0.32	0.46
	4	0	>0.05	−0.32	0.32
	3				
	1	−0.57	>0.05	−1.19	0.05
	2	−0.07	>0.05	−0.46	0.32
	4	−0.07	>0.05	−0.29	0.15
	4				
	1	−0.5	>0.05	−1.13	0.13
	2	0	>0.05	−0.32	0.32
	3	0.07	>0.05	−0.15	0.29
Extension	1				
	2	0.14	>0.05	−0.15	0.44
	3	0.42	0.04	0.002	0.85

Contd...

Table 2: Contd...

Outcome	Time	Mean difference score	P^+	95% CI for difference	
				Lower bound	Upper bound
	4	0.42	0.04	0.002	0.85
	2				
	1	−0.14	>0.05	−0.44	0.15
	3	0.28	>0.05	−0.1	0.67
	4	0.28	>0.05	−0.1	0.67
	3				
	1	−0.42	0.04	−0.85	−0.002
	2	−0.28	>0.05	−0.67	0.1
	4	0	>0.05	0	0
	4				
	1	−0.42	0.04	−0.85	−0.002
	2	−0.28	>0.05	−0.67	0.1
	3	0	>0.05	0	0

$^+$Wilcoxon signed-rank test. FASI=Facial angiofibroma severity index, CI=Confidence interval

Table 3: Relationship between the difference in erythema score, size, extension, and facial angiofibroma severity index, with history of seizures, the presence of cephalic fibrosis plaque, and education (the ability to study) index, 12 weeks after treatment compared to the baseline (*n*=14)

Variable	Mean difference of outcome (12 weeks after-baseline), mean±SD							
	Erythema	P^+	Size	P^+	Extension	P^+	FASI score	P^+
History of seizure								
Yes	−0.63±0.67	0.86*	−0.45±0.68	0.29*	−0.36±0.5	0.36*	−2.18±1.16	0.38*
No	−0.66±1.15		−1±1		−0.66±0.57		−3±2.64	
Cephalic fibrosis plaque								
Yes	−0.75±0.95	0.81*	−0.5±01	0.63*	−0.25±0.5	0.41*	−2±1.82	0.65*
No	−0.6±0.69		−0.6±0.69		−0.5±0.52		−2.5±1.43	
Education								
Yes	−0.66±0.77	0.84*	−0.58±0.79	1*	−0.5±0.52	0.2*	−2.5±1.56	0.3*
No	−0.5±0.7		−0.5±0.7		0		−1.5±0.7	

*P>0.05, $^+$Mann–Whitney U-test. FASI=Facial angiofibroma severity index, SD=Standard deviation

significant relationship between the mean score of erythema, size, extension and FASI and the number of Ash leaf macules in patients. Except for erythema score, with increasing number of Ash leaf macules, mean score of size, extension and FASI increased after 3 months of treatment compared to before treatment (respectively, Spearman's Rho = −0.16, Rho = 0.28, Rho = 0.22, Rho = 0.27, $P > 0.05$).

Discussion

In current study we evaluate the efficacy and safety of topical timolol 0.5% in the treatment of FA in children with tuberous sclerosis. Timolol is a nonspecific beta blocker with antiangiogenesis effect such as: 1-Inhibition of renin to angiotensin two conversion, which angiotensin 2 is the formation factor of vascular endothelial growth factor (VEGF). VEGF converts the vascular endothelial basal cells to vascular endothelial cells.

2-Metalloproteinase 9 matrix is effective in angiogenesis and is inhibited by beta-blockers 3-reduced angiogenesis through production of osteoprotegerin.[10]

The reported treatments for angiofibroma are cryotherapy, radiofrequency ablation, shave excision, electrodesiccation, dermabrasion, ablative fractional laser. It can cause many complications including scar, Hyperpigmentation and pain and have more than 80% recurrence.[10]

Topical rapamycin is another treatment that seems to be effective, although it requires longer studies. Laser of lesions accompanied with topical treatment such as timolol and Rapamycin can be more effective. Rapamycin has become very popular in the treatment of angiofibroma and in the treatment of lesions smaller than 4 mm alone can be sufficient.

Rapamycin is such an expensive drug that it may take several hundred to several thousand dollars to get enough results. Beta-blockers have been used for

vascular lesions for several years. Oral propranolol has been effective in treating hemangiomas in the pediatric population. Timolol 0/5% as a solution or gel, 2–3 times a day, has effectively treated superficial hemangiomas.[10]

In a study by Krakowski and Nguyen which is reported as a case report in 2015 in American Academy of pediatric, topical timolol 0.5% has been used to treat FA in a patient with tuberous sclerosis. This study has shown significant improvement of angiofibroma.[8]

In another study conducted in 2017 on topical timolol in the treatment of infantile hemangiomas, published in the American academy of dermatology, topical timolol is effective on infantile hemangioma lesions that are small and superficial.[13]

Another study in 2018 showed that beta-blockers have been influential in treating skin lesions of vascular origin and wound healing. It is also mentioned that this treatment is very cheap and inexpensive that can be used to treat many skin lesions, as our study showed.[12]

In another study conducted by Al Mokadem *et al*. in 2020, topical timolol on the treatment of acne and rosacea was investigated. In this study, which was performed on 116 patients, the use of topical 0.5% timolol every night before bed on the lesions for 8 weeks was very effective in treating acne, especially noninflammatory type. It was more effective on erythematous telangiectasia rosacea than papulopustular rosacea, which in our study was effective on angiofibroma lesions.[20]

Authors' contribution

Mohammadreza Ghazavi, Omid Yaghini, and Bahareh Abtahi-Naeini contributed to the concept of the study and definition of intellectual content. Bahareh Abtahi-Naeini, Sareh Taheri, Ali Mohammad Sabzghabaee, and Gita Faghihi contributed to the study design. Negah Tavakolifard contributed to data analysis and statistical analysis. Sareh Taheri and Kimia Afshar contributed to literature search, clinical studies, experimental studies, and data acquisition. Ali Mohammad Sabzghabaee contributed to drug preparation. Sareh Taheri and Bahareh Abtahi-Naeini contributed to manuscript preparation.

All authors contributed to manuscript editing and review.

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Conflicts of interest

There are no conflicts of interest.

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