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Clinical Evaluation Of The Topical Timolol Efficacy And Safety In The Treatment Of Infantile Hemangioma

Mustafa Hazim Ahmed[1] , Shakir Al-Saedy[2] and Ahmed Yahya Abbas[3]*

[1,2]Dermatologist and veneriologist, CABMS, Al-Kindy teaching hospital, Baghdad, Iraq.

[3*]Dermatologist and veneriologist, CABD, Marjan medical city, Babil, Iraq.

ahmed_yahya87@yahoo.com

Abstract

Background: Infantile hemangiomas are the most common childhood soft tissue tumors. More than 50% of them occur in the head and neck region. As spontaneous regression occurs over years, active intervention is needed only for large complicated hemangiomas. But, even small uncomplicated hemangiomas in visibly prominent area like face can be emotionally disturbing to parents. Even after reassurance of spontaneous regression, often parents are not ready to wait for years to see the beautiful smile on their child's face.

Objectives: To evaluate the effectiveness and safety of topical timolol in Iraqi infants with hemangioma.

Patients & Methods: This prospective and clinical therapeutic study was conducted in Al-Kindy Teaching Hospitalin Baghdad – Iraq during the period between the beginning of September-2018 to the end of the October - 2019. A total of 28 infants with infantile hemangiomas were included in this study. They were treated with topical timolol maleate 0.5% ophthalmic solution applied at a dose of 1 drop for each 1 cm2 surface area of the lesion under occlusion by simple wound plaster twice daily before feeding for 16 weeks period of therapy. Changes in the length, width, thickness and color of the hemangiomas were recorded at regular interval. The response to treatment was evaluated by periodic clinical examination of hemangioma at 4th week, 8th week and at the end of 16th week of treatment. The results were interpreted by two methods; overall response rate in which the color, the size and the thickness were measured serially to identify the growth, and visual analogue scale in which two independent dermatologists were asked for their opinion about the response to treatment which was expressed in term of three classes; class 1, ineffective, class 2, controlled growth and class 3, promoted regression. The regression rate was percentage of patients with class 3, while efficacy rate was the sum percentage of patients with class 2 and class 3.

Results: This study showed thattopical timolol induced reduction in length, width, thickness and color in all treated 28 patients by the end of 16 weeks treatment course. By visual analogue scale, the treatment showed 85.7% regression rate and 96.4% efficacy rate for the same above mentioned treatment course. Complete ulcer healing of the 4 patients with ulcerated hemangiomas documented in the study was noticed without the need

for use of other topical treatment for the ulcers. No major side effects were reported in treated children .None of the treated hemangioma was recurrent after cessation of treatment for a follow up period of 4 months.

Conclusion: Topical timololmaleate 0.5% solution is found to be an effective and safe treatment of infantile hemangiomasand, adding the fact that patients in this study did not receive any previous treatment for their hemangiomas, can be considered as a safe and effective first line therapy for cutaneous infantile hemangiomas.

Key words: infantile hemangioma, timolol,

Declarations:

Acknowledgement:

We render our special thanks to all doctors and paramedical staff in Al-Kindi Teaching Hospital for their help, time and openness during data collection.

Conflict of interest:

The authors declare that there is no conflict of interest.

Contributions:

1) Ahmed Yahya Abbas collected data, drafted and wrote the manuscript, interpreted and discussed the results. Also oversaw the final version of the paper and agreed to be (corresponding author).
2) Mustafa Hazem Ahmed designed the study and participated in data collection.
3) Shakir Al-Saedycritically reviewed the manuscript to evaluate the content.

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Ethics approval and consent to participate:

The research was approved after the adoption of the protocol by ethical committee of Al-Kindy Teaching hospital, Ministry of Health, Iraq. In addition Approval was taken from Dermatology Scientific Committee of Arab board. Confidentiality was assured with informed consent from all the patients.

Introduction

Infantile hemangiomas are common, benign, usually self-limiting endothelial cells tumors of infancy; they are proliferative lesions, usually appears during the first weeks of life [1,2]. They

have a unique biphasic growth behavior [2,3] . The unique growth characteristic of hemangioma can be divided into 3 phases [2] :

- Proliferation phase.

-Involuting phase.

-Involuted phase.

The phase of rapid growth is usually most pronounced during the first 3 to 6 months, followed by a phase of slower growth, between the middle and end of the first year of life[3,4]. The involutional phase of an infantile hemangioma may be rapid or prolonged. No specific characteristics appear to influence the rate or completeness of involution of infantile hemangiomas[1,3] , 50-70% percent of infantile hemangiomascomplete involution by age 5 -7 years ,the remainder may take an additional 3-5 years to complete the process.

A first step in management of infantilehemangiomas is to identify whether it is a low-risk /uncomplicated or high-risk/complicated hemangioma[15,17].A hemangioma that is asymptomatic, small in size, non-ulcerated and does not have the potential to impair a vital function is called low-risk or uncomplicated hemangioma. For these forms of lesion, it is generally enough to observe them.

Treatment should be considered in the following circumstances [21,23] :

- Very large and unsightly lesions
- Ulcerating haemangiomas (up to 5-25% of lesions)
- Lesions that impair vision, hearing, breathing or feeding
- If they fail to resolve by school age

The possible treatments include[23 , 26 , 27] :

- External compression therapy (bandaging the limbs)
- Ultrapotent topical steroids.
- Topical antiseptics. Eosin, which also has antiangiogenic properties, has been reported to be of benefit.
- Oral corticosteroids in high dose, during the proliferative stage of segmental disease.
- Sometimes, intralesional steroid injections have been used for small haemangiomas.
- Vascular laser therapy at age 3 to 4 years, when lesions are stable

- Interferon alpha may be useful but is rarely recommended, as it has been associated with the development of cerebral palsy in a few infants.
- Vincristine was reported effective in the past but is rarely used today
- Imiquimod has been reported to speed resolution in some cases.
- Oral propranolol is an emerging alternative to systemic steroid and the only FDA approved treatment.[33, 35]
- Topical timolol is rapidly becoming the treatment for cutaneous non complicating hemangiomas and is the subject of several current research trials.[44]

Patients and Methods

This prospective, clinical therapeutic study was conducted in Al-Kindy Teaching Hospital during a period from the beginning of September-2018 to the end of the October-2019. The study included 28 infants (23 females; 5 males) presented with 28 IHs of different types, at different body regions.

Every patient was subjected to a thorough history taking and physical examination to ascertain risk factors or contraindications to using beta-blockers. Specific questions pertaining to reactive airway disease, asthma, lung or heart problems, hypoglycemia, and reflux are asked. Parents were thoroughly given a complete discussion about how infantile hemangioma grows in phases, possible treatment modalities, and side effects. Baseline electrocardiograms (ECG) are conducted and interpreted by a pediatric cardiologist for all treatment candidates. Prior cardiac history, suspected heart blocks, or other abnormal findings on ECG warrant an echocardiogram prior to therapy initiation.

Inclusion criteria were as follow:

1. Age less than or equal to 12 months.

2. Single cutaneous hemangiomas diagnosed according to Werner and Suen 1999 classification criteria [47].

3. No history of prior treatment.

4. No evidence of short term regression.

Exclusion criteria comprised:

1. Age more than 12 months.

2. Prior treatment with other modalities.

3. Evidence of short term regression.

4. Any history of cardiovascular disorders, bronchial asthma, insulin dependent diabetes mellitus, recent or repeated outbreak of wheezing and visceral haemangioma**.**

Ethical approval was confirmed from Scientific Council of Dermatology and Venereology Arab board for Medical Specializations.

After obtaining written informed consent from the parents, topical treatment was started with timolol maleate 0.5% ophthalmic solution applied at a dose of 1 drop for each 1 cm^2 surface area of the lesion under occlusion by simple wound plaster twice daily before feeding for 16 weeks period of therapy. First dose was given to the patients in dermatology department, and the application procedure had been demonstrated to the mother who repeated it again in front of us to be certain for the next doses.

In the absence of side effects, treatment was continued at home, and infants were reevaluated on weekly basis at first month, every 2 weeks in the second month, and then every month till the end of treatment after 4 months. Finally, all infants were followed up for up to 4 months after cessation of timolol treatment. Despite the fact that topical timolol has minimum, if any, side effects on skin application, mothers were informed about signs of beta blockers side effects like fainting, restless sleep, irritability and mood disturbance.

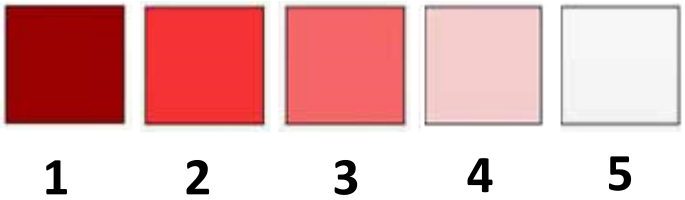
All patients were subjected, in each visit, to full evaluation including clinical exanimation of hemangiomas to assess the response and possible side effects of beta blockers.

Baseline photograph was carried out before starting treatment as well as at each follow-up visit using high resolution Nikon D5100 digital camera 24 megapixels.

The response to treatment was evaluated by periodic clinical examination of hemangioma at 4^{th} week, 8^{th} week and at the end of 16^{th} week of treatment. The results were interpreted by two methods:

1. Overall response rate: The color, the size and the thickness were measured serially to identify the growth. Size was measured by a ruler in two dimensions; thickness was identified by the height from nearby normal skin to the highest

point in the lesion, while color was assessed according to color scale from 1 to 5, as shown in the figure below:



2. Visual analogue scale: Two independent dermatologists were asked for their opinion about the response to treatment which was expressed in term of three classes:
   - **Class 1, ineffective:** the lesion continued to grow.
   - **Class 2, controlled growth:** the lesion stopped growing but showed no significant changes in size, color or thickness.
   - **Class 3, promoted regression:** the lesion became smaller, thinner and lighter in color.

The regression rate represented the percentage of cases with class 3 results, while the efficacy rate represented thepercentage of cases with class 2 or class 3 results.[48]

Statistical analysis:

Results were presented in numbers, percentages, mean values ± SD, and ranges. Data were statistically analyzed using ANOVA test (ANalysis Of VAriance) by the Statistical Package for Social Sciences (SPSS software v. 20) and statistical significance was set at $P \leq 0.01$.

Results

Patients' characteristics:

During the period from beginning of September 2013 till the end of October 2014, a total of twenty eight infants attended the department of Dermatology and venereology in Al-Kindy Teaching Hospital in Baghdad were diagnosed as infantile hemangiomas and included in this study. Their mean ages were 5.96 months, ± SD of 2.46 months and a median of 5.5 months (Table -1).

Table (1): Age distribution of patients

Age (months)	Number	%
2-	1	3.6

3-	**3**	**10.7**
4-	**5**	**17.9**
5-	**5**	**17.9**
6-	**4**	**14.3**
7-	**3**	**10.7**
8-	**2**	**7.1**
9-	**2**	**7.1**
10-	**1**	**3.6**
11- 12	**2**	**7.1**
Total	**28**	**100.0**

Females represented 82.14% of the sample (23 infants), while the rest 5 (17.86%) were males with female to male ratio 4:1 (Table -2). Family history for hemangioma was positive in 7.14 %. Mean age of onset was 1.96 weeks and **±** SD of 0.88 weeks and none of the infants had hemangioma at birth. (Table -3)

Table (2): Gender distribution of patients

Gender	Number	%
Female	**23**	**17.86**
Male	**5**	**82.14**
Total	**28**	**100.0**

Table (3): Patients' distribution according to age of onset

Age of onset (weeks)	Number	%
First week	**9**	**32.14**
Second week	**13**	**46.43**
Third week	**4**	**14.29**
Fourth week	**2**	**7.14**
Total	**28**	**100.00**

Lesions' characteristics:

Lesions of various types, locations, sizes and thicknesses were included in the study with a unique feature of being cutaneous hemangiomas without associated visceral counterparts.

Twenty three (82.14%) lesions were of superficial type (capillary infantile hemangioma) and only 5 (17.86%) were mixed ones (having both superficial and deep elements). Head and neck were the commonest site of involvement (13 (46.43%)), followed by the trunk (8 lesions (28.57)) and extremities (5 lesions (17.86)), while genitalia came last in the rank by only 2 (7.14%) lesions (Table -4).

Lengths (the longest diameter of the lesions) ranged from 8 to 80 millimeters with a mean of 32.39 mm; width's range was 5 – 60 millimeters and a mean of 22.57 mm, while thickness ranged from 1 to 7 millimeters with a mean of 3.11 mm (Table -5).

Ulceration at presentation was noticed in 4 (14.29%) cases, two of them were on the genitalia and the other two were on the trunk and upper extremity.

Table (4): Types and locations of infantile hemangiomas

Infantile hemangiomas' data		N	%
Types	Superficial	23	82.14
	Mixed	5	17.86
	Total	28	100.0
Locations	Head and Neck	13	46.43
	Trunk	8	28.57
	Extremities	5	17.86
	Genitalia	2	7.14
	Total	28	100.0

Table (5): Lesions' characteristics

Parameter	Range (mm)	Mean	SD
Length	8 – 80	32.39	20.90
Width	5 - 60	22.57	14.17
Thickness	1 - 7	3.11	1.59

According to the color scale, most of the lesions (18 (64.29%)) were under scale 1 (deep red) at initial presentation, while 9 (32.14%) lesions had scale 2 (bright red). Scale 3 (faint red) was the feature for only one (3.57%) lesion in the sample (Table-6 and Figure - 4).

Table (6): Color scale of the lesions

Scale	Number	%
1 (Deep red)	18	64.29
2 (Bright red	9	32.14
3 (Faint red)	1	3.57
4 (Gray white)	0	0.00
5 (White or skin color)	0	0.00
Total	28	100.00

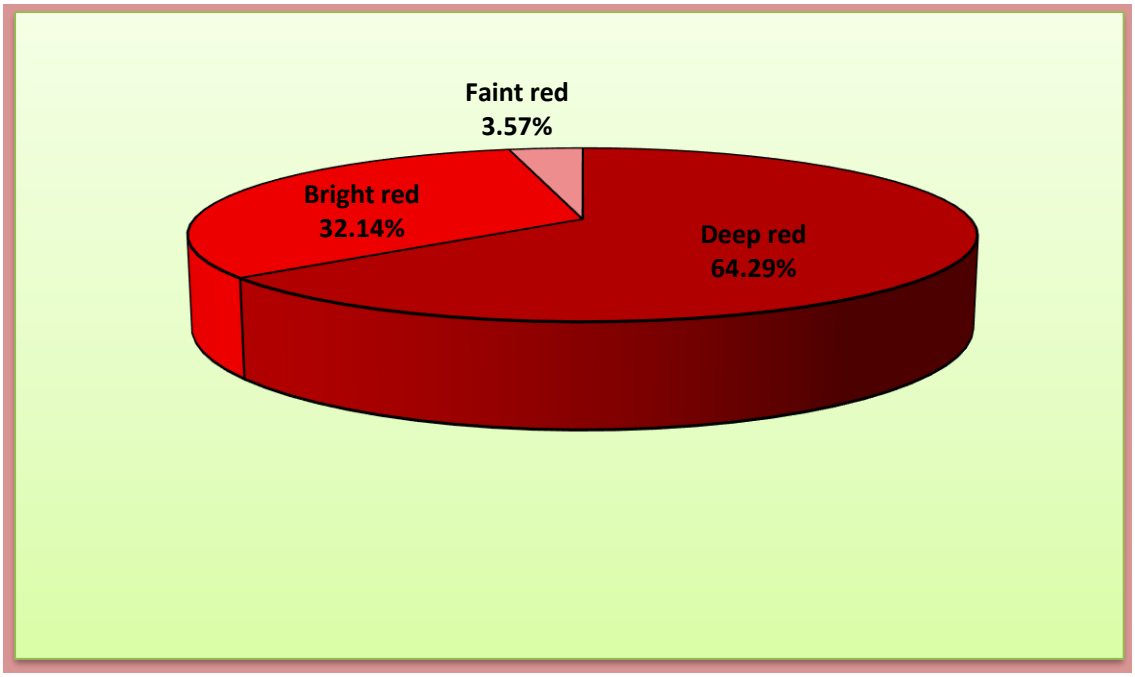


Figure (4): Color scale of lesions at initial presentation

Response to topical timolol therapy:

Change in the color depth of hemangiomas was the early clinical response to topical timolol therapy that occurred within the first 2 weeks of treatment. The color change was from deep to bright red and from bright to faint red according to the initial color at presentation. Flattening and size regression occurred later in the course of treatment.

Changes in the length of the lesion:

During the first visit after starting treatment, i.e. after 4 weeks, twenty one (75%) patients showed measurable reduction in the length of the lesion which was considered to be the longest diameter, six (21.43%) showed no change in length and only 1 (3.57%) exhibited increased growth. These data were left shifted during the second visit (after 8 weeks of starting therapy) where 27 (96.43%) patients showed marked reduction in the length and only 1 (3.57%) patient remained unchanged. The third visit (16 weeks later) showed reduction in length of all lesions. This was statistically significant at P = 0.01 by ANOVA test (Table-7).

Table (7): Response to treatment assessed by length of lesion

Visits	Decreased		No change		Increased		Total
	n	%	n	%	n	%	

4 weeks	21	75.00	6	21.43	1	3.57	28	100.0
8 weeks	27	96.43	1	3.57	0	0.00	28	100.0
16 weeks	28	100.00	0	0.00	0	0.00	28	100.0

ANOVA TEST						
Level	N	Mean	SD	DF	F	P value
Baseline	28	32.39	20.91	3	8.61	< 0.01
4 weeks	28	27.86	20.22			
8 weeks	28	19.75	16.44			
16 weeks	28	10.43	9.85			

Changes in the width of the lesion:

Nearly similar observations were noticed regarding the width of lesions during the first visit where 23 (82.14%) patients showed decreased width, 4 (14.29%) unchanged and 1 (3.57%) increased. The second and third visits were exactly similar to those seen in the length assessment and also statistically significant at p = 0.01 (Table-8 and figure-5).

Table (8): Response to treatment assessed by width of lesion

Visits	Decreased		No change		Increased		Total	
	n	%	n	%	n	%		
4 weeks	23	82.14	4	14.29	1	3.57	28	100.00
8 weeks	27	96.43	1	3.57	0	0.00	28	100.00
16 weeks	28	100.00	0	0.00	0	0.00	28	100.00

ANOVA TEST						
Level	N	Mean	SD	DF	F	P value

Baseline	28	22.57	14.17	3	13.41	< 0.01
4 weeks	28	19.18	13.44			
8 weeks	28	13.14	9.76			
16 weeks	28	5.07	3.93			

Changes in the thickness of the lesion:

Regarding thickness changes, the first visit showed thickness reduction in 17 (60.71%) patients, no change in 9 (32.14%) and increment in 2 (7.14%) which, during the second visit, changed to 23 (82.14%), 4 (14.29%) and 1 (3.57%) respectively. This was ended, in the third visit, with thickness reduction in all patients (figure-6). Statistically, ANOVA test revealed that thickness reduction was highly significant with a P value less than 0.01 (Table-9).

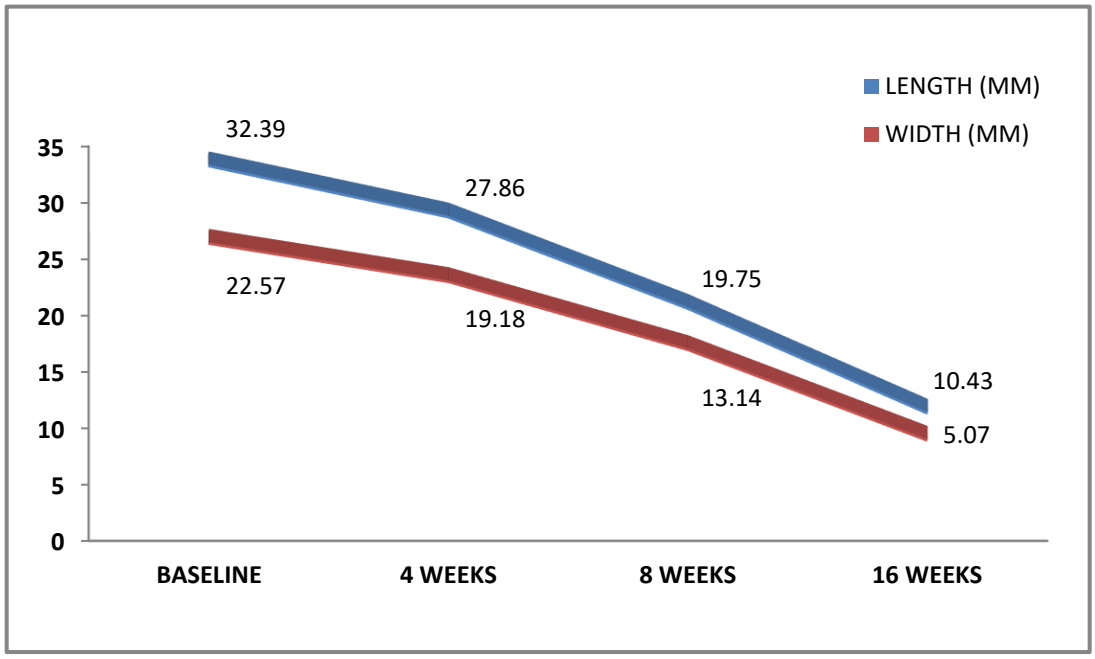


Figure (5): Mean changes in length and width of lesions over the three visits of the study.

Table (9): Response to treatment assessed by thickness of lesion

Visits	Decreased	No change	Increased	Total

	n	%	n	%	n	%		
4 weeks	17	60.71	9	32.14	2	7.14	28	100.00
8 weeks	23	82.14	4	14.29	1	3.57	28	100.00
16 weeks	28	100.00	0	0.00	0	0.00	28	100.00

ANOVA TEST

Level	N	Mean	SD	DF	F	P value
Baseline	28	3.19	1.57	3	14.72	< 0.01
4 weeks	28	2.56	1.55			
8 weeks	28	1.85	1.43			
16 weeks	28	0.85	0.065			

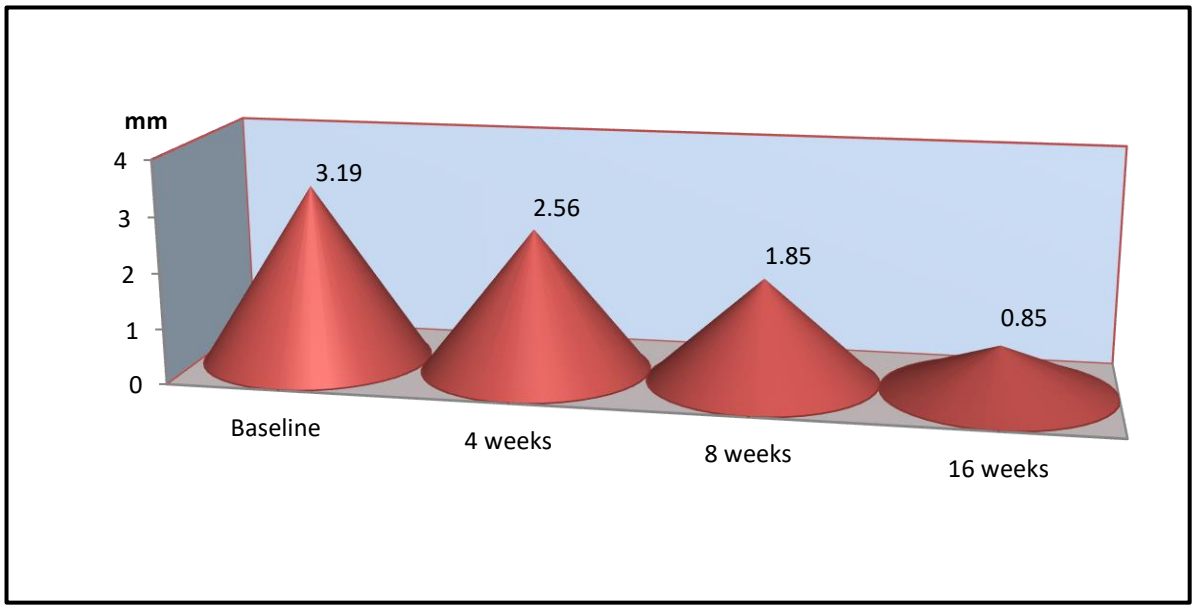


Figure (6): Mean changes in thickness of lesions over the three visits of the study.

Changes in the color of the lesion:

Color changes were the most encouraging results, where 21 (75%) patients showed decreased color intensity and 7 (25%) patients exhibited the same color during their first

visit. None of them experienced increased color intensity. This was followed, in the second visit, by decreased color intensity in all the 28 patients, which continued with the same result till the third visit (Table-10).

Table (10): Response to treatment assessed by color change

Visits	Decreased		No change		Increased		Total	
	n	%	n	%	n	%		
4 weeks	21	75.00	7	25.00	0	0.00	28	100.00
8 weeks	28	100.00	0	0.00	0	0.00	28	100.00
16 weeks	28	100.00	0	0.00	0	0.00	28	100.00

ANOVA TEST						
Level	N	Mean	SD	DF	F	P value
Baseline	28	1.39	0.57	3	99	< 0.01
4 weeks	28	2.18	0.55			
8 weeks	28	2.89	0.63			
16 weeks	28	4	0.61			

Changes in visual analogue scale:

Visual analogue by two independent dermatologists during the first visit showed that 14 (50%) patients were categorized under class 3 (promoted regression), 11 (39.29%) patients under class 2 (controlled growth) and 3 (10.71%) patients were considered ineffective or class1. The second visit showed some increase in class 3 (18 (64.29%)), and some decrease in both class 2 (8 (28.57%)) and class 1 (2 (7.14%)). A clear satisfaction was apparent at the third visit when the two dermatologists categorized 24 (85.71%) patients under class 3 and 3 (10.71%) under class 2, while only 1 (3.57%) patient was considered to get no benefit from the treatment (class 1)(figure - 7). These results were statistically significant at P = 0.01 level (Table – 11).

Table (11): Response to treatment assessed by visual analogue scale

Visits	Class 1 Ineffective		Class 2 Stopped growth		Class 3 Promoted regression		Total	
	n	%	n	%	n	%		
4 weeks	3	10.71	11	39.29	14	50.00	28	100.00
8 weeks	2	7.14	8	28.57	18	64.29	28	100.00
16 weeks	1	3.57	3	10.71	24	85.71	28	100.00

ANOVA TEST						
Level	N	Mean	SD	DF	F	P value
4 weeks	28	2.39	0.69	2	3.55	< 0.01
8 weeks	28	2.57	0.63			
16 weeks	28	2.82	0.47			

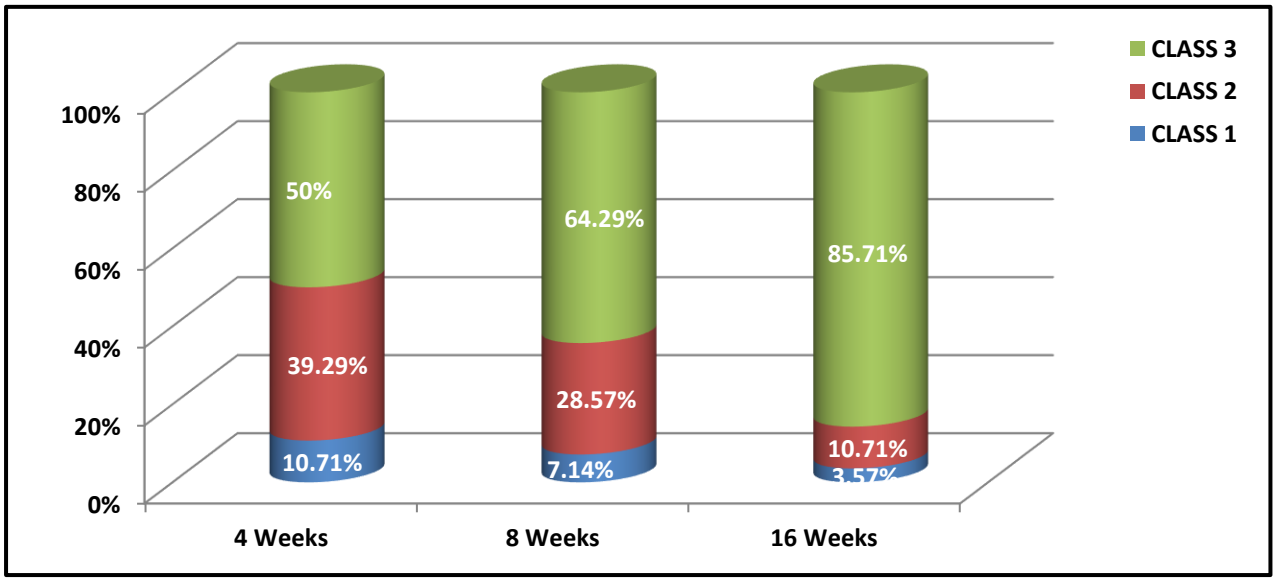


Figure (7): Class percentages of visual analogue scale during the three visits

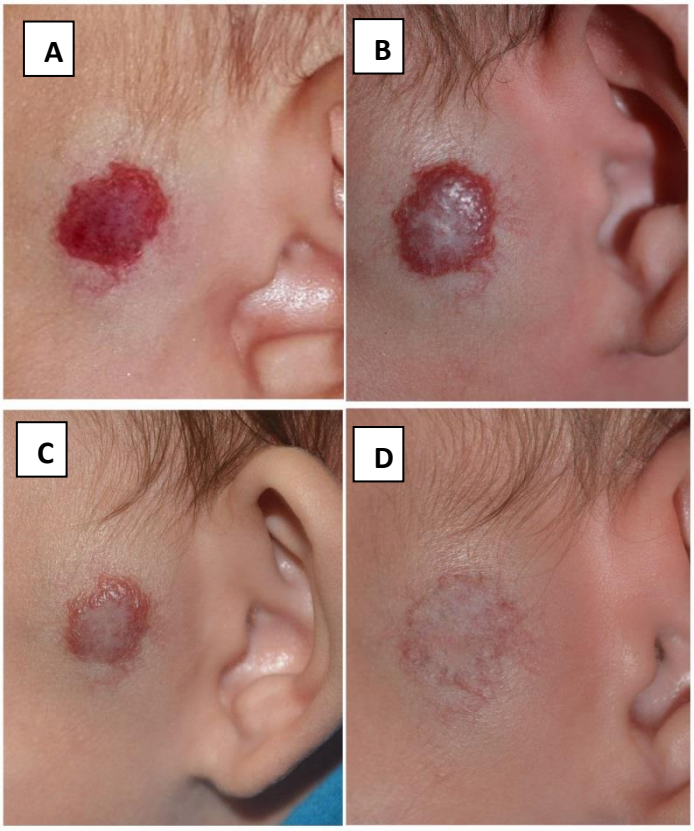


Figure (8): Response of infantile hemangioma to topical timolol 0.5% solution in 4 months old male infant A. Before treatment, B. 4 weeks after, C. 8 weeks after and D. 16 weeks after starting treatment

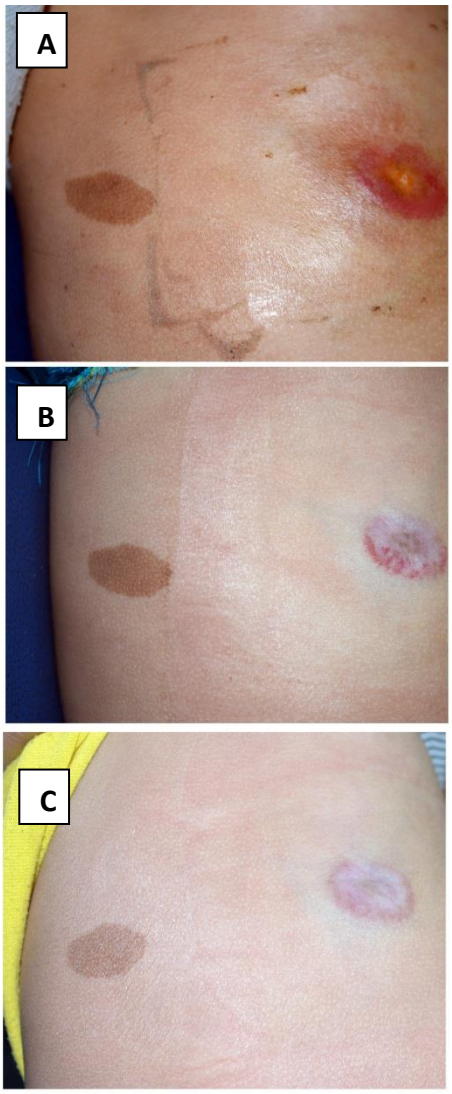


Figure (9): Response of infantile hemangioma to topical timolol 0.5% solution in 3 months old female infant A. Before treatment, B. 4 weeks after, C. 16 weeks after starting treatment

ign tumor composed of hyperplastic vascular endothelium. cy are common, benign, self-limited tumors [8], although, it is progress and prognosis of hemangioma during the first few e unpredictable outcome after proliferation and proposed iomas, and because there is no way to predict the size that gnificant percentage of hemangiomas are associated with

substantial morbidity in infancy and childhood such as disfigurement, psychosocial distress for patient and family and threats to life or function, that is why therapeutic interventions are frequently indicated in many cases [2,3].

Despite many treatments that have been described for the treatment of hemangiomas, there is no currently well-studied or FDA approved systemic therapy for infantile hemangiomas except for propranolol. The US Food and Drug Administration (FDA) have approved a pediatric formulation of propranolol hydrochloride for treatment of proliferating infantile hemangioma requiring systemic therapy [49]. There is a controversy concerning the safety of systemic propranolol. Here we show that topical use of the beta-blocker timolol can also inhibit the growth and promote regression of infantile hemangiomas.

Recently, several reports of successful treatment of infantile hemangiomas with topical timolol maleate, in forms of gel and solution, have been published which was described for the first time in 2011 by Nina, Langer and Wagner, medical ophthalmologists, when they used topical timolol for the treatment of periocularhemangioma.[50] Yet, little is known about the proper dosing, mode of administration and long-term outcomes, in addition to the small sample size of several published studies where the conclusions are neither scientifically nor statistically solid.

Timolol is thought to exert its effect on hemangioma by two mechanisms; vasoconstriction and antiangiogenic effects. Timolol, as β-adrenoceptor antagonist, inhibits vasodilatation mediated by adrenaline leading to vasoconstriction with subsequent reduction of blood flow within the lesions resulting in reduction in the depth of the color of treated hemangioma that is reported to be the first sign of clinical response occurring within first 14 days of starting therapy.

Timolol, as β-receptor blocker, leads to a reduced expression of pro-angiogenic factors: vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) on endothelial cells which are increased during proliferation of hemangiomaleading to inhibition of angiogenesis with the subsequent decrease in the size of hemangioma and flatting of the lesion with further reduction in the depth of its color, this possibly explains the marked reduction in the size of the treated hemangioma within the first few weeks of treatment and their significant regression.

A total of twenty eight infantswere diagnosed as infantile hemangiomas and included in this study, their mean ages were 5.96 months, ± SD of 2.46 months and a median of 5.5 months. Age of less than 12 months was the first inclusion criteria in this study. This was done in purpose to solidify the results of the study since, as it is mentioned in the introduction, hemangiomas has their maximum rate of growth during the first year of life after which it starts to involute during the next few years. This will make us believe that when there is regression or involution in the size of treated hemangiomas, it will be due to the drug effect and not due to the natural history of hemangioma, i.e. to eliminate the natural history of the lesion as a cause for the regression.

Change in the color depth of hemangiomas was the early clinical response to topical timolol therapy that occurred within the first 2 weeks of treatment. This response time is earlier than similar study which required 4 to 8 weeks to notice the color changes in the lesions.[50]

This response was seen in 75%, and then in 100%, of treated patients by first and second visits respectively. The color change was from deep to bright red and from bright to faint red or skin color tone according to the initial color at presentation.

Despite the variable outcomes noticed during the first and second visits, the third visit, after completing 16 weeks of treatment, showed a 100% reduction in length, width, thickness and color of the lesions under treatment.

The rate of response that have been reported in the present study is slightly higher than that of other studies using the same treatment regimen, such as the Egyptian study done by Genedy et al which showed 80% partial response and 20% excellent response in the treated patients[51].

Much higher response rate have been achieved in this study than that of other studies, using different treatment type. Hermanset al showed that 60% of their patients had complete resolution of the lesion with the use of 2 mg/ kg/ day oral propranolol in 3 equally divided doses [52]. In addition, this study achieved a higher response rate than that reported by Holmes et al using higher dose of propranolol (3 mg/ kg/day) with response rate (87%).[53]

None of the treated patients in this study were resistant to treatment or did not respond to topical timolol therapy, in contrast to that reported by other studies which used oral propranolol as the remedy for hemangiomas.**[53, 54]**

Also, responses were consistent on long-term follow up. None of the patients in the present study showed evidence of recurrence or rebound growth of hemangiomas (increase in the size or worsening of the color) after cessation of therapy for a minimum of 4 months follow up period in comparison with other studies in which the rebound growth was reported.[54, 55]

The subjective response to treatment was measured by the visual analogue scale in which two independent dermatologists were asked for their opinion about the response to treatment which was expressed in term of three classes:

Class 1, ineffective: the lesion continued to grow.

Class 2, controlled growth: the lesion stopped growing but showed no significant changes in size, color or thickness.

Class 3, promoted regression: the lesion became smaller, thinner and lighter in color.

By end of treatment i.e. after 16 weeks, regression rate (percentage of patients categorized under class 3) was 85.7% and efficacy rate (sum percentage of both class 2 and 3) was 96.4%. These results were higher than a similar study done in China which followed the same procedure in response measurement. The regression rate in the Chinese study was 56.4% and the efficacy rate was 92.1% despite the frequency of application was three times daily.[48]

The efficacy rate reported by this study was also higher than another study done by Chambers et al, who used 0.25% timolol maleate gel, in which the efficacy rate was 92.3% and recorded consistent responses on long-term follow up also.[56]

Both superficial and mixed lesions responded well to treatment except for one mixed lesion was considered to be ineffective by the visual analogue scale.

Four ulcerated hemangiomas were present in this study; all of them showed complete healing of their ulcers without the use of traditional ulcer remedies such as topical antibiotics.

The marked good response and lack of recurrence indicate that timolol achieved permanent resolution of hemangiomas, which occur earlier than the expected resolution through the natural course of the disease which is said to be completed by the age of 5 -7

years in 50-70 % of the cases, in addition to the risk of disfigurement and complication that may be serious and interferes with the function of vital organs.

Although the fair response is reported in 10.7%of the cases , but we thought that, topical timolol achieved another goal of treatment as it induces gradual re-epithelialization of ulcerated hemangioma with complete resolution of symptoms that was achieved with in the first 4 weeks of treatment .In addition, ultimate reduction in ugly looking hemangioma , reducing the interference of hemangiom with the function of vital organ with satisfaction of parents of treated child achieved a remarkable reduction in the psychological impact of the child hemangiom on his parents which we think is an important outcome of any used medication. Moreover, the partial response to topical timolol in this study is probably comparable, if it is not better, than that of other modalities of treatment for such type of hemangioma.

In addition, we think that topical timolol is useful when given prior to other therapeutic modalities, to reduce the size of hemangioma, thus making it more amenable to treat with surgery, laser and other options to achieve better result.

Moreover, unlike other studies that have shown successful response of ulcerated hemangiomas to oral propranolol , none of the patients in present study had received any previous therapy prior to topical timolol treatment for ulcerated hemangioma, where at least one of the following treatment modalities including: topical and/or systemic antibiotics , pulsed dye laser therapy , or oral corticosteroids has been used prior to starting therapy with propranolol [55, 57] , so this makes the present study superior than others in this point, because the clinical improvement of ulcerated hemangioma in the present study is attributed only to the action of topical timolol .

In this study, none of the patients showed serious side effects neither during the treatment, nor during follow up period.

Exclusion of patients with personal or family history of cardiac and respiratory diseases, in addition to exclusion of older age groups and multiple hemangiomas, had limited the number of the sample to be included in this study.

Conclusions

1. At therapeutic doses, 1 drop / 1 cm^2 twice a day before feeding for 16 weeks , topical timolo is shown to be a safe and effective treatment of infantile

hemangioma with significant improvement and minimum, if any, risk of the side effects in addition to poor chance of recurrence after cessation of treatment.

2. Early treatment of hemangioma with topical timolol associated with significant clinical response and remarkable improvement in comparison with late one.
3. Even in partially responding hemangioma , timolol was found to accelerate healing of ulceration , thus reducing the ugly looking of infantile hemangioma , so achieving better satisfaction of the parents of the treated child.
4. Adding the fact that patients in this study did not receive any previous treatment for their hemangiomas, topical timolol can be considered as a safe and effective first line therapy for cutaneous non complicating infantile hemangiomas.

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