Topical Beta Blockers as a Treatment for Superficial Cutaneous Infantile Haemangiomas

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Abstract: IH is a pediatric vascular tumor that appears as red, raised flesh a few weeks after birth in 5-10 % of neonates, and it is more common in the prematurely-born and in females. Infantile hemangioma (IH) is one of the most common benign tumors of childhood, with an incidence of between 4% and 10%. Topical application of timolol maleate, a non-selective β-blocker, is efficacious for the treatment of IHs, especially small superficial lesions. The use of topical beta blockers for hemangiomas is a relatively new indication for an old drug that has rapidly been accepted by the medical community, particularly those in pediatric specialities. The mechanism of action is being elucidated, but currently is thought to involve multiple pathways. Early reports find efficacy with minimal risk to the child, particularly when compared to the potential side effects of corticosteroids. A consensus on the preparation, dose, and duration of treatment would be beneficial. Similarly, a method of standardizing reporting of treatment success would improve analysis of future publications. In this study the age of initiation of treatment was more than eighteen months in twenty patients while sixteen patients had the onset of their treatment before twenty four months of age, four patients started the treatment after twenty four months of age, twelve patients who are less than twenty four months of age had 50% at least or more improvement of their hemangiomas (Good response) while only four patients had less than 50% improvement in their hemangiomas. On the other hand four patients who started their treatment after twenty four months of age had less than 50% improvement in their hemangiomas (Poor response). We suppose Topical Timolol maleate is a successful line of treatment for small superficial infantile hemangioma.

[Mosaad Mohammed El Behery, Ahmed Ain Shoka, Mohammed Said El Sherbeny, Emad Eldeen Mamdouh El Deghedy**. Topical Beta Blockers as a Treatment for Superficial Cutaneous Infantile Haemangiomas.** *Nat Sci* 2019;17(12):1-9]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 1. doi:10.7537/marsnsj171219.01.

Keywords: Topicalp; Beta Blocker; Treatment; Superficial; Cutaneous; Infantile; Haemangiomas

1. Introduction

Haemangiomas are the most common tumors of infancy. The true incidence of infantile haemangiomas is unknown. Although they are classically said to occur in up to 10 percent of Caucasian infants, 4 to 5 percent is probably a better estimate. Infantile haemangiomas are generally noticed within the first few days to months of life ***(Kilcline and Frieden, 2008)***.

Although most haemangiomas occur sporadically, familial transmission in an autosomal dominant fashion has been reported. In one series of 136 patients/families, 34 percent had a family history of infantile haemangiomas, most often in first-degree relatives ***(Castrén and Salminen, 2016)***.

Known risk factors include low birth weight, Caucasian ethnicity, female gender, advanced maternal age, and a variety of prenatal complications including placenta previa and pre-eclampsia ***(Haggstrom et al., 2007)***.

The exact pathogenesis of Infantile Haemangioma is incompletely understood, though markers not expressed in normal dermal or subcutaneous tissues are frequently detected in IH. In particular, vascular endothelial growth factor (VEGF), glucose transporter-1 (GLUT-1), and placenta-associated vascular antigens (i.e., FcγRII, merosin, and Lewis Y antigen) are highly expressed in the endothelial cells of IH throughout both the rapid growth phase and the involution phase. Interestingly, the only other vascular tissue known to share a similar expression profile is from placental chorionic villi. Some current experimental evidence proposes that IH may derive from clonal proliferations of endothelial cells through the de novo formation of primitive blood vessels from angioblasts ***(Barnés et al., 2005)***.

Increased numbers of mast cells and levels of tissue metalloproteinase (an inhibitor of new blood vessel formation), upregulation of interferon- induced genes, and decreased quantities of fibroblast growth factor (FGF) have been identified as potential molecular mediators of IH involution (***Ritter et al., 2006)***.

Infantile haemangiomas are common, particularly in female, white children of low birth weight, with approximately 6% affected. They are

often present at birth, although may not be noticed until a few weeks later when the lesion begins its proliferative phase. The lesions grow rapidly in the first few months of life before stabilizing and finally involuting. There are no reliable indicators to predict the degree and rate of involution ***(Skrobal and Haderer, 2014)***.

The mainstay of therapy for IH is active nonintervention (i.e., watchful waiting) as most lesions are uncomplicated and will in volute Spontaneously without significant sequel ***(Metry and Hebert, 2000)***.

First reported on the use of topical treatment for Infantile Haemangioma using a non-selective beta-blockers solution and the curative effect was obvious ***(Guo et al., 2010)***.

Timolol maleate used topically is effective and safe for treating superficial haemangiomas. We began to treat then with timolol maleate applied topically in October 2012 ***(Ye et al., 2012)***.

Aimof the Work

The aim this study was to evaluate the role of topical beta-blocker solution (Timolol maleate 0.5%ml gel forming solution) in the treatment of superficial cutaneous infantile hemangiomas.

2. Patients and Methods

This prospective randomized study included 20 patients with hemangioma attending the clinic of pediatric surgery in Ain Shams University hospitals and Benha children hospital.

Inclusion Criteria:

Pediatric patients aged between 18 months and 5 years with superficial cutaneous infantile haemangioma.

Exclusion Criteria:

Patients who underwent previous form of treatment for infantile haemangioma.

Patients who diagnosed with extra cutaneous hemangiomas.

Patients with deep infantilehemangiomas.

Pulmonary disease such as bronchialasthma.

Cardiac disease such as heart failure or AV block.

Diabetes mellitus.

History of impaired kidney or liver function.

Patients with previous treatment of hemangioma.

Hypersensitivity to Timolol.

Informed consent signed by responsible parents with approval of medical treatment was done for all patients.

All patients were subjected to the following:

Pre-treatment work-up:

Detailed history taking.

Thorough clinical examination to assess any associated congenital anomalies.

Cardiovascular work-up:

This was done with the help of paediatric cardiololgists and involved baseline clinical observations (pulse, blood pressure respiratory rate, weight and height) and Echocardiogram.

Routine laboratory investigation:

- Complete blood picture, Liver and Kidney functions.
- Blood glucose level.

Determination of the location and dimensions of hemangioma based on direct measurement and photographicanalysis.

Radiological assessment using Doppler US as baseline data as regard: site, size, depth, vascularity and flow.

The patients were treated with Timolol maleate drops 0.5% (TIMOLOL 0.5% eye drops, NILE) for four months under treatment & two months follow up and evaluation.

The parents were instructed to apply with a fingertip one drop per cm2 onto the surface of the haemangioma five times daily, and gently rub it in.

The first application of timolol took place at the hospital. Pulse and blood pressure were measured 30 min after this application and at every visit thereafter.

Parents were informed about the possible side effects and for what clinical signs and symptoms they should look for during the treatment.

Treatment was discontinued and the patient was excluded from the study if there was:

a. Fall of heart rate to 70% of baseline.
b. Symptomatic bronchospasm.
c. Symptomatic hypoglycemia.

Follow up:

All patients were followed up for a period of 6 months from treatment initiation.

Visits were held every 2 weeks in the first month then monthly over the next 3 months with adjustment of dosage according to changes of weight every month.

Duration of therapy was 6 months (four months under treatment & two months follow up and evaluation).

In each visit:

a) Full clinical examination including all vital signs was done.

b) Parents were asked about possible side effects caused by betablockers.

c) Recording the dimensions of hemangioma based on direct measurement (in millimeters and 2 axes) and standard digital photographic analysis using same camera and obtained by same person.

Doppler US was carried out at the end of the study and compared to the initial baseline data.

All patients completed the full four month course of treatment, and the drug was therefore discontinued,

with no relapse during the two month follow-up period.

Outcome:

Response to treatment was evaluated as follows: [Table]

Excellent: more than 75%regression.
Good: 50% to 75%regression.
Poor: 25% to 50%regression.
No response: less than 25% or no regression.

Response to treatment was evaluated upon following criteria:

Decrease in the dimensions of hemangioma either clinical or radiological.

Lightening of color. (Gradual whitish discoloration)

Flattening of surface.

Radiologic improvement.

Regression degree	Definition
Excellent	75 – 100 % regression in volume (Near total disappearance).
Good	50 – 75% regression in volume (Greater than50 percent reduction in volume).
Poor	25 – 50% regression in volume (Definite reduction in volume but less than 50 percent).
No response	0-25% regression in volume (Little or no reduction in size).

3. Results

Table (1): Distribution of the studied cases according to demographic data (n= 20):

	No.	%
Age (months)		
≤24	16	80.0
>24	4	20.0
Min. – Max.	18.0 – 36.0	
Mean ± SD.	22.20 ± 4.70	
Median	21.0	
Sex		
Male	8	40.0
Female	12	60.0
BMI (kg/m^2)		
Normal	16	80.0
Low	4	20.0

The study included one group composed of 20 patients, subjected to Timolol maleate drops 0.5% applied three times a day by rubbing carefully on hemangioma.

Treatment for this group was continued for a period of three months.

This table shows demographic data in our study population (n=20).

In our sample, age ranged from 18 to 36 months with mean of 22.20 ±4.70.

There were 16 patients of the whole population with age ≤24 (80 %), and 4 patients with age >24 (20 %).

There were 8 male patient in our sample (40 %) and 12 female patients (60 %).

History of low birth weight was present in 4 patients (20 % of the total population) while the remaining 16 patients were within normal range of BMI.

As regard the history, 4 patients with history of prematurity were found in our sample and 2 patients had twins one had a brother and the other had a sister.

According to family history, 4 patients were found to have positive family history of hemangiomas.

Table (2): Distribution of the studied cases according to perinatal History and family history (n =20):

	No.	%
Perinatal History		
Preterm	4	20.0
Full Term	14	70.0
Twin	2	10.0
Family History		
Negative	16	80.0
Positive	4	20.0

Table (3) shows that the subtype of hemangioma. Eighteen patients (90%) had only one region affected by hemangioma while two patients (10%) had more than one region affected by hemangioma.

Table (3): Distribution of the studied cases according to number (n = 20):

Number	No.	%
Single	18	90.0
Multiple	2	10.0

According to site of hemangiomas, table (4) shows the different sites were found in our sample. The head and neck region constituted 75% of infants with hemangiomas, distributed in the form of two hemangiomas (10%) in the scalp, one (5%) in the lip, one (5%) periorbitalone, four (20%) in the forehead, and four (20%) in the nose. Other areas constituted five patients (25%) with two patients (10%) in the abdomen, two (20%) in the buttock and only one (5%) in the back.

Table (4): Distribution of the studied cases according to location (n = 20):

Location	No.	%
Head and neck		
Scalp	2	10.0
Lip	1	5.0
Periorbital	1	5.0
Forehead	4	20.0
Cheek	3	15.0
Nose	4	20.0
Ear lobule	0	0.0
Other areas		
Abdomen	2	10.0
Finger	0	0.0
Buttocks	2	10.0
Back	1	5.0

Table (5) shows comparison between pretreatment and post treatment length (in mm) of previously measured hemangiomas. They ranged in pretreatment between 6.0 – 30.0 with a mean of 17.43 ± 9.24 while, in post treatment, they ranged between 4.0 – 28.0 with a mean of 11.40 ± 6.83. The reduction in length was calculated with a mean of 6.03 ± 5.63. There was a statistically significant reduction in length of hemangioma (p value <0.001) after treatment with Timolol.

Table (5): Comparison between pre and post according to length:

Length	Pre-Treatment	Post-Treatment	Z	p
Min. – Max.	6.0 – 30.0	4.0 – 28.0		
Mean ± SD.	17.43 ± 9.24	11.40 ± 6.83	3.927*	<0.001*
Median	16.50	10.0		
Change	↓6.03 ± 5.63			

Z: Wilcoxon signed ranks test, p: p value for comparing between pre and post
*: Statistically significant at p ≤ 0.05

Table (6) shows comparison between pre and post treatment width of hemangiomas. The pre treatment width found ranged between 11.0 – 37.0 with a mean of 20.85 ± 7.53 while the post width ranged between 6.0 – 30.0 with a mean of 14.45 ± 7.05. The reduction in width was calculated with a mean of 6.40 ± 5.24. There was a statistically significant reduction in the width of hemangioma (p value <0.001) after treatment with Timolol.

Table (6): Comparison between pre and post according to width:

Width	Pre-Treatment	Post-Treatment	Z	p
Min. – Max.	11.0 – 37.0	6.0 – 30.0		
Mean ± SD.	20.85 ± 7.53	14.45 ± 7.05	3.827*	<0.001*
Median	20.0	12.0		
Change	↓6.40 ± 5.24			

Z: Wilcoxon signed ranks test
p: p value for comparing between pre and post
*: Statistically significant at p ≤ 0.05

Table (7) shows comparison between pre and post treatment size. The pretreatment size measured clinically (in mm2) ranged between 66.0 – 1110.0withameanof420.85±337.21whilethepostsizeranged between

30.0 – 840.0 with a mean of 206.10 ± 229.69. The reduction in size was calculated with a mean of 214.75 ± 244.97. There was a statistically significant reduction in the size of hemangioma (p value <0.001) after treatment with Timolol maleate drops 0.5% applied three times a day by rubbing carefully on hemangioma.

Table (7): Comparison between pre and post according to size:

Size	**Pre-Treatment**	**Post-Treatment**	**Z**	**p**
Min. – Max. Mean ± SD. Median	66.0 – 1110.0 420.85 ± 337.21 330.0	30.0 – 840.0 206.10 ± 229.69 123.0	3.920*	<0.001*
Change	↓214.75 ± 244.97			

Z: Wilcoxon signed ranks test, p: p value for comparing between pre and post *: Statistically significant at p ≤ 0.05

According to the response to treatment Excellent response to treatment was defined as regression in volume of hemangiomas which ranged between 75-100 %, good as between 50-75 %, fair as between 25-50% and poor 0- 25% regression in volume as shown in table (8).

In our sample, 3 patients (15%) showed excellent response, 9 patients (45%) showed good response, 4 patients (20%) showed poor response and 4 patients (15%) showed no response.

Table (8): Distribution of the studied cases according to response (n = 20):

Response	**No.**	**%**
No response (<25)	4	20.0
Poor (25 – 50)	4	20.0
Good (50 – 75)	9	45.0
Excellent (75 – 100)	3	15.0

There was an obvious difference in the response according to the age of initiation of the treatment as shown in table (9) where good responses (which included good and excellent responses were found to be more when the age of initiation of treatment was less than twenty four months. We had twelve (60%) patients in the sector of good response, all of them were twenty four months or less (Statistically significant at p ≤0.05).

While, poor response were eight (40%) patients, four (50%) of them were more than twenty four months and the other four (50%) were twenty four months or less.

According to sex, our sample showed no difference in response between male and female. We had eight (40%) patients in the poor sector, two (25%) were males and six (75%) were females.

While in the good sector, we had twelve (60%) patients, six (50%) were males and six (50%) were females.

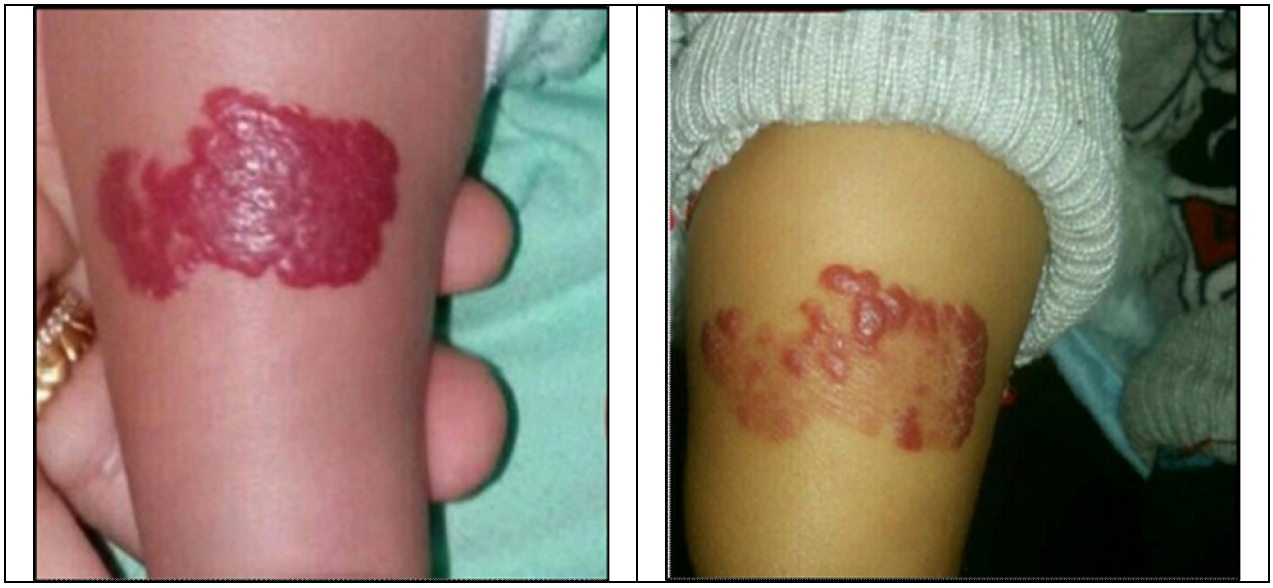
Table (9): Relation between response and different parameters (n= 20):

	Response				**Test of sig.**	**p**
	Poor response (n= 8)		**Good response (n= 12)**			
	No.	**%**	**No.**	**%**		
Age (months) **≤24** **>24**	 4 4	 50.0 50.0	 12 0	 100.0 0.0	^{2}=7.500*	FEp= 0.014*
Min. – Max. **Mean ± SD.** **Median**	18.0 – 36.0 25.63 ± 5.53 25.0		18.0 – 24.0 19.92 ± 2.11 19.0		t=2.789*	0.023*
Sex **Male** **Female**	 2 6	 25.0 75.0	 6 6	 50.0 50.0	^{2}=1.250	FEp=0.373

^{2}: Chi square test, FE: Fisher Exact t: Student t-test

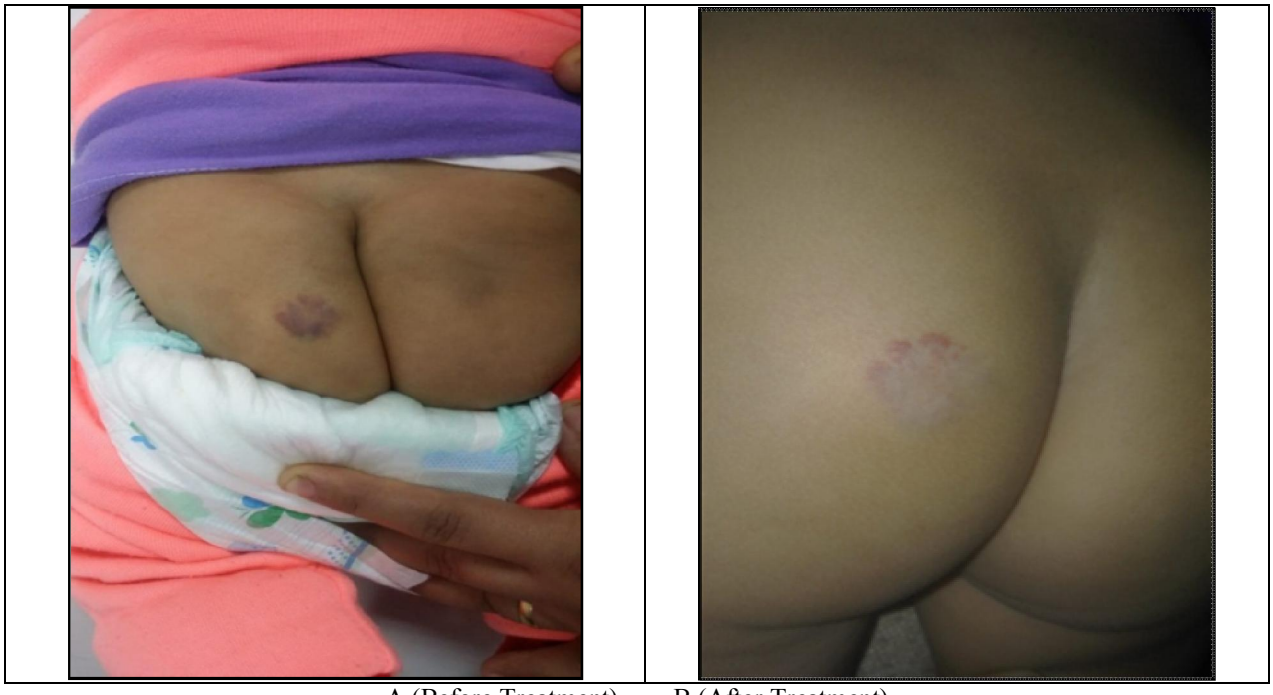
p: p value for association between response and different parameters

*: Statistically significant at p ≤ 0.05



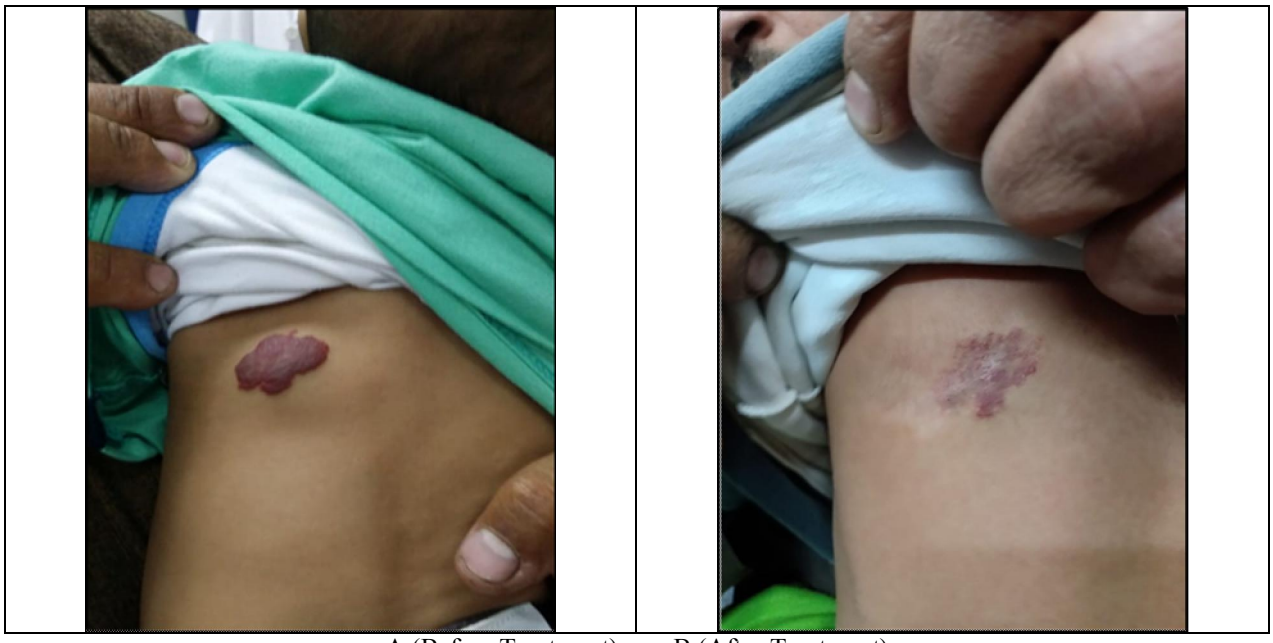
A (Before Treatment) B (After Treatment)

Case (1): Female patient aged 20 months, treated with Timolol maleate 0.5%ml gel forming solution for 4 months and 2 months follow up.



A (Before Treatment) B (After Treatment)

Case (2): Male patient aged 21 months, treated with Timolol maleate 0.5%ml gel forming solution for 4 months and 2 months follow up.



A (Before Treatment) B (After Treatment)

Case (3): Female patient aged 24 months, treated with Timolol maleate 0.5%ml gel forming solution for 4 months and 2 months follow up.

4. Discussion

The mainstay of therapy for IH is active non-intervention as most lesions are uncomplicated and will involute spontaneously without significant sequel.

At some point, typically by the second year of life, unknown triggers halt the proliferation and increase the rate of apoptosis, marking the transition into the involution phase.

After the first case-report published in 2010 by Guo et al., regarding the utility of topical beta blockers in hemangioma, especially timolol maleate, several case reports and some studies were described. The results were encouraging, timolol maleate seems to induce regression in the superficial component of hemangiomas and it could be a substitute when systemic propranolol is contraindicated ***(Luu and Frieden, 2013; Tavakoli et al., 2017)***.

Two papers compare topical beta blockers to untreated controls ***(Chambers et al., 2012; Su et al., 2018)***. Yu and coworkers compared 101 patients treated with timolol versus 23 observed children. They created their own classification system: class 1, the lesion continued to grow; class 2, the lesion stopped growing; class 3, the lesion became smaller, softer, and lighter in color. In the treatment group, 36% of lesions were in class 2 and 57% in class 3 compared to 30% of controls in class 2 and 4% of controls in class 3. This was statistically significant ***(Su et al., 2018)***.

Chamberscompared13patientstreatedwithtimolol 0.25%gelversus

10 observed patients. There was a statistically significant difference in outcome between the 2 groups, with only 1 patient failing to show a decrease in size with treatment versus 9 in the observed group. The patient who failed to show a response had a purely deep lesion ***(Chambers et al., 2012)***.

Two papers compare beta blockers to placebo ***(Chan et al., 2013; Wargon, 2013)***.

Chan treated small, superficial lesions to analyze timolol 0.5% maleate gel versus placebo, using relative change in predicted volume of the hemangioma to ascertain an effect.

Their results were that 16 weeks of treatment are required to see a statistically significant difference in size between treatment and placebo. Photographs taken at 12 weeks after treatment onset do not show a significant difference in response, whereas those taken at 24 weeks are statistically significant.

These results suggest a lengthy treatment is required to produce a clinical response, most likely secondary to the low dose regime (1 drop twice a day) that was used ***(Chan et al., 2013)***. This long period required to see a treatment response is not duplicated in any other study reviewed for this article.

Wargon compared 0.5% timolol maleate gel versus placebo and found statistically significant color change on blinded photographic scores and statistically significant reduction in volume of lesions in 41 infants ***(Wargon, 2013)***.

There are currently no commercially available forms of topical propranolol; however, intraocular preparations of b-blockers used for glaucoma exist.

In this study the age of initiation of treatment was more than eighteen months in twenty patients while sixteen patients had the onset of their treatment before twenty four months of age, four patients started the treatment after twenty four months of age, twelve patients who are less than twenty four months of age had 50% at least or more improvement of their hemangiomas (Good response) while only four patients had less than 50% improvement in their hemangiomas. On the other hand four patients who started their treatment after twenty four months of age had less than 50% improvement in their hemangiomas (Poorresponse).

With topical Timolol therapy, the therapeutic efficacy is observed within a few days of treatment onset. Lesions are noted to be softer, less purple in color, and less elevated. Lesions then begin to reduce in size until completely flat or disappeared. Timolol has any effect on fibro-fatty residua. The pharmacokinetics of cutaneously applied timolol has not been studied in detail. Studies on the pharmacokinetics and beta-blocking effects of transdermal timolol patches (5% timolol, 0.2 mg ⁄ cm2) found plasma concentration levels to be below the detection limit after application for 48 h ***(Kubota et al., 1993)***.

Consistent with the latter, in our study and in the other reported cases, timolol has to date not produced any systemic adverse reactions when used to treat IHs in the available formulations of 0.1% and 0.5% ***(Pope and Chakkittakandiyil, 2010; Blatt et al., 2011)***.

Oral propranolol is known to cause hypoglycemia, and this has been reported in those with hemangiomas. Hypoglycemia has the potential to be more profound in young children whose glycogen stores are limited ***(Zhavoronkov et al., 2012)***. This has not been reported in any children treated with topical medication.

In Ni's early report using timolol solution, patient's heart rates

Preadministration and postadministration of medication were checked, and parents checked heart rates at home ***(Ni et al., 2011)***. No changes in heart rate were noted.

Xu and coworkers measured echocardiogram, blood pressure, heart rate, and blood sugar before treatment, after 1 week and then every 4 to 8 weeks thereafter ***(Xu et al., 2012)***. No side effects were noted. Chan measured blood pressure and heart rate before treatment and throughout the study period ***(Chan et al., 2013)***. No hypotension or brady cardia was noted in 19 patients.

Caution should be exercised when timolol is used in the periorbital area because of the increased absorption via the conjunctiva and therefore the potential for increased side effects.

Nevertheless, the available safety data are still insufficient, and dermatologists should be alert for the known side-effects of beta-blockers and thus monitor infants accordingly.

Many clinicians have taken their own approach to dose regimens. The patients were treated with Timolol maleate drops 0.5% (TIMOLOL 0.5% eye drops, NILE). The parents were instructed to apply with a fingertip one drop per cm2 onto the surface of the haemangioma five times daily. In Chakkittakandiyil and Pope's multicentre study of 73 patients, timolol 0.1% GFS was compared to timolol 0.5% GFS. By using the visual analogue scale (VAS), they showed that children treated with 0.1% timolol had a mean VAS improvement of 24 29, whilst those treated with 0.5% timolol had a mean improvement of 48 28 (P ¼ 0.01). There was a statistically significant difference in treatment response; however, neither hemangiomasize nor onset of treatment was factored into the analysis ***(Chakkittakandiyil et al., 2012)***.

Oranje published a pilot study of timolol 0.1% gel applied either 3 or 4 times daily and found it to be less effective than timolol 0.5% ***(Oranje et al., 2011)***. Semkova found that 0.1% gel 5 times daily was beneficial in all patients, suggesting that increased frequency is key to success with lower concentrations ***(Semkova and Kazandjieva, 2013)***.

Our study had several limitations; the procedures for digital photography were not uniformly standardized, the investigators were not blinded to duration of treatment, and the main outcome measure relied on one indicator only that, although previously used, has not been validated for IH assessments. Dosage, inclusion criteria, and strict definitions of superficial and deep IH were not standardized, size of IH was not included in factors determining response to treatment, and treatment was initiated at various stages in the natural course of the disease.

Despite its limitations, this study demonstrates further clinical evidence of the efficacy and tolerability of topical timolol gel-forming solution applied twice a day in patients with superficial IH. It also provides data that will enable power calculation and proper design methodology for prospective studies trying to confirm the safety and efficacy of this treatment modality.

Conclusion

The use of topical beta blockers for hemangiomas is a relatively new indication for an old drug that has rapidly been accepted by the medical community, particularly those in pediatric specialities. The mechanism of action is being elucidated, but currently is thought to involve multiple pathways. Early reports find efficacy with minimal risk to the child, particularly when compared to the potential side

effects of corticosteroids. A consensus on the preparation, dose, and duration of treatment would be beneficial. Similarly, a method of standardizing reporting of treatment success would improve analysis of future publications.

We suppose Topical Timolol maleate is a successful line of treatment for small superficial infantile hemangioma.

References

1. Barnés CM, Huang S, Kaipainen A, et al: Evidence by molecular profiling for a placental origin of infantile hemangioma. Proc Natl Acad Sci USA. 2005;102(52):19097-102.
2. Blatt J, Morrell DS, Buck S, et al: beta-blockers for infantile hemangiomas: a single-institution experience. Clin Pediatr (Phila). 2011 Aug;50(8):757–63.
3. Castrén E, Salminen P, Vikkula M, et al: Inheritance Patterns of Infantile Hemangioma. Pediatrics. 2016;138(5): e20161623.
4. Chakkittakandiyil A, Phillips R, Frieden IJ, et al: Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. Pediatr Dermatol. 2012;29(1):28–31.
5. Chambers CB, Katowitz WR, Katowitz JA, et al: A controlled study of topical 0.25% timolol maleate gel for the treatment of cutaneous infantile capillary hemangiomas. Ophthal Plast Reconstr Surg. 2012;28(2):103–6.
6. Chan H, McKay C, Adams S, et al: RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. Pediatrics.2013;131(6):e1739-47.
7. Guo S and Ni N: Topical treatment for capillary haemangima of the eyelid using beta-blocker solution. Arch Ophthalmol. 2010;128 (2):255-6.
8. Haggstrom AN, Drolet BA, Baselga E, et al: Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr. 2007;150(3):291–4.
9. Khunger N and Pahwa M: Dramatic response to topical timolol lotion of a large hemifacial infantile haemangioma associated with PHACE syndrome. Vol. 164, The British journal of dermatology. England; 2011. p. 886–8.
10. Kilcline C and Frieden IJ: Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25(2):168-73.
11. Kubota K, Yamada T, Kikuchi K, et al: Pharmacokinetics and beta-blocking effects of transdermal timolol. Eur J Clin Pharmacol. 1993;44(5):493–5.
12. Luu M and Frieden IJ: Haemangioma: clinical course, complications and management. Br J Dermatol. 2013 Jul;169(1):20–30.
13. Metry DW and Hebert AA: Benign cutaneous vascular tumors of infancy: when to worry, what to do. Arch Dermatol. 2000;136(7):905- 14.
14. Ni N, Langer P, Wagner R, et al: Topical timolol for periocular hemangioma: report of further study. Vol. 129, Archives of ophthalmology (Chicago, : 1960). United States; 2011. p.377–9.
15. Oranje AP, Janmohamed SR, Madern GC, et al: Treatment of small superficial haemangioma with timolol 0.5% ophthalmic solution: a series of 20 cases. Dermatology. 2011;223 (4):330–4.
16. Piotrkowska R: Porównanieopiniirodzicównatematjakościżyciadziecile czonych z powodunaczyniaków. 2015.
17. Pope E and Chakkittakandiyil A: Topical timolol gel for infantile hemangiomas: a pilot study. Vol. 146, Archives of dermatology. United States; 2010. p. 564–5.
18. Ritter MR, Reinisch J, Friedlander SF, et al: Myeloid cells in infantile hemangioma. Am J Pathol. 2006;168(2):621-8.
19. Semkova K and Kazandjieva J: Topical timolol maleate for treatment of infantile haemangiomas: preliminary results of a prospective study. Clin Exp Dermatol. 2013;38(2):143–6.
20. Skrobal M, Haderer L, Preiml Y, et al: Aprospective epidemiological study of infantile haemangioma in an Austrian referral tertiary centre. J Ger Soc Dermatol.2014; (23):E21.
21. Su R, Dong L, Li C, et al: R-2HG Exhibits Anti-tumor Activity by Targeting FTO/m (6)A/MYC/CEBPA Signaling. Cell. 2018;172(1– 2):90–105.e23.
22. Tavakoli M, Yadegari S, Mosallaei M, et al: Infantile Periocular Hemangioma. J Ophthalmic Vis Res. 2017;12(2):205–11.
23. Wargon O: Randomised placebo controlled trial: Safety and efficacy of topicaltimolol maleate gel vs placebo for small superficial infantile haemangiomas. Vol. 54, Australasian Journal of Dermatology. 2013. 22-23p.
24. Xu G, Lv R, Zhao Z, et al: Topical propranolol for treatment of superficial infantile hemangiomas. J Am Acad Dermatol. 2012;67(6):1210–3.
25. Ye XX, Jin YB, Lin XX, et al: Topical timolol in the treatment of periocularuperficial infantile haemangiomas. Aprospective study. Zhonghua Zheng Xing Wai Ke Za Zhi. 2012;28(3):161-4.
26. Zhavoronkov A, Smit-Mc Bride Z, Guinan KJ, et al: Potential therapeutic approaches for modulating expression and accumulation of defective lamin A in laminopathies and age-related diseases. J Mol Med (Berl).2012;90(12):1361–89.

8/17/2019