



Infantile Hemangioma and Effect of Timolol in Its Regression, an Hospital Based Study at Maternity and Child Hospital Sopore, North India

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Abstract

Objective: To study and assess the effect of of Timolol maleate (0.5%) in superficial infantile haemangioma of eyelid and other areas in children's through topical application.

Methods: An retrospective hospital based interventional study carried out at maternal and child hospital(MCH) north india, 51 cases attending paediatric outpatient department at MCH Sopore were included in study after detailed clinical examination.

Results: Most of infantile haemangioma were superficial and localised. Significant regression in infantile haemangioma size was seen after treating the cases with topical timolol maleate (0.5%). Common indication of therapy was disfigurement risk, We included 51 subjects in this study, out of which 60.7% were females and 39.3% were males, regarding site of involvement Head-and-neck involvement was seen in 47 % of the infants, the trunk was involved in 33.3% of the infants, the limbs were involved in 19.7 % of t Response to treatment with timolol was excellent in 63 % of the infants, Better in 20 % of the infants, Considerable in 13 % of the infants, good in 4 % of the infants, and none of the infants showed minor response. While as adverse effects like poor feeding and sleep disturbances due to topical timolol were not seen in our study.

Conclusion: Topical timolol maleate (0.5%) is considerably effective and safe treatment in infantile haemangioma, therefore can be recommended for superficial and small infantile hemangiomas due to very less adverse effects.

Keywords: Infant, Capillary haemangioma, Topical timolol maleate 0.5%, Response rate.

INTRODUCTION

Infantile haemangioma (IH) are common benign vascular tumours of infancy, occurring in 3 to 10% infants(1,2) .60% of Infantile haemangiomas occur in head and neck region followed by 25% occurring in trunk and 15 % on extremities (3). Most haemangioma appear on the skin surface and are bright red. These are called superficial infantile

haemangioma and are sometimes called "strawberry birthmarks. "or "strawberry naevi"now these replaced are replaced by vascular tumour,. They are characterised by three phases i.e rapid proliferative phase (6 to 12 months), followed by period of gradual involution and then regression phase ranging from 4 to 9 years(4) Most of infantile haemangioma regress

spontaneously and require no treatment(5) while only 10% require intervention(6).

Female babies are more affected than males in the ratio of 3-5:1 (7), while as caucasians(8), Preterm babies with a birth weight of < 1Kg are at higher risk of 23% (9). Advanced maternal age, pre-eclampsia, placenta previa and positive family history respectively have been reported with Infantile haemangioma(10,11). Besides this non-selective β -blocker, Timolol can be used topically in solution or gel form, emerged as a novel agent(12) in treatment of infantile haemangioma (Zheng and Li, 2018). Moreover topical use of beta-blocker has been reported as valid alternative, particularly superficial IH (13). In addition, In 2010 Guo & Ni presented successful first report of topical timolol treatment in a resolving infantile haemangioma in 4 month old infant (14). After that various case series and case reports have reported efficacy of topical timolol, thereby making topical timolol as main treatment modality in superficial IH (15). Moreover treatment of infantile haemangioma by using topical solution of timolol maleate is mainly evidence based from observational studies and from clinical expertise, rather than from randomized controlled trials (16).

The current study analyses the safety and efficacy of topical timolol maleate(.5%) in treatment of cutaneous superficial IH in north Kashmir India, above all intervention should be initiated in early proliferative phase to avoid complications like ulceration, disfigurement, haemorrhage and stress on parents and involved children's.

Methods:

Inclusion criteria:

Willing attendants of infants.

1. Infants
2. Cutaneous Superficial Haemangioma over face, eyelids and ears.
3. Prior treatment not received.
4. Tumour thickness ≤ 3 mm
5. No evidence of short-term regression.

Children with bronchial asthma, sinus bradycardia and second- or third-degree atrioventricular block were not excluded from the study.

1. The exclusion criteria comprised:
2. Unwilling parents of patients.
3. age >12 months;
4. Previous treatment.
5. tumor thickness >3 mm and
6. Evidence of tumor regression in the short-term.

Informed consent was taken from parents of study group and they were properly informed about the treatment given for infantile haemangiomas and also the adverse effects although minimal. Timolol maleate (0.5%) drops i.e 2- 3 drops were used and applied twice daily and Vaseline used around haemangioma to prevent leaking into surrounding skin. Follow up of patients was done every month upto six months and photographs were taken on every visit patients to see tumour size and all the patients were asked to note the regression in haemangioma using subjective assessment score. Doppler ultrasound of haemangioma was done in all the patients who were affording before the start of the treatment to differentiate between haemangioma and vascular malformations. Institutional ethics committee approval was obtained prior to initiation of the study colour, besides this on every follow up treatment response to topical timolol was recorded.

While as response to treatment was seen as flattening of lesion, surface lightening and regression in size. At each visit, Global assessment scale (range between -1 to +4) was used to see the treatment response in terms of haemangioma regression as described below:

- Excellent response – >90% haemangioma regression
- Better response – Between 75% and 90% decrease in size of haemangioma
- Considerable response – Between 50% and 74% haemangioma regression.
- Good response – Between 25% and 49% regression of haemangioma
- Minor response – <25% decrease in size of haemangioma.

Also parents of patients were educated to note haemangioma regression by using subjective assessment score. In order to differentiate between haemangioma and vascular malformations Doppler

ultrasound of all patients was done before initiating treatment.

Results:

The present study based on 51 cases of infantile haemangioma attending pediatric OPD at maternal and child hospital ,J&K India during a period of 3

years from 1st January 2017 to December 2019, who underwent treatment with topical 0.5% timolol maleate for infantile haemangiomas. out of 51 cases 31(60.7%) were females and 20(39.3%) were males . Regression was expressed in terms of frequency and percentage, while as P value ($P < 0.05$) was considered statistically significant.

Table 1: Gender distribution of Infantile Haemangioma Patients

Gender	Frequency(N)	Percentage (%)	P-Value
Female	31	60.7	
Male	20	39.3	0.123
Total	51	100	

Table 2: Location of Haemangioma

Distribution	Frequency(N)	Percentage (%)	P-Value
Head and Neck	24	47	
Trunk	17	33.3	0.123
Lower Extremities	10	19.7	
Total	51	100	

Table 3: Response to application of topical timolol maleate (0.5%) in Infantile Haemangioma

Response	After 8 wks of	After 16 weeks		Percentage (%)	P -Value
Treatment		Frequency(N)			
Excellent	12	18	30	58.8	↓
Better	4	6	10	19.6	
Considerable	2	5	7	13.7	<0.005
Good	1	3	4	7.8 (significant)	↑
Minor	Nil	Nil	Nil	Nil	

Photograph 1: Showing Better response to topical Timolol in Infantile Haemangioma.



Photograph 2: Showing Excellent response to topical timolol in Infantile Haemangiomas





Photograph 3: Showing Excellent response to topical Timolol in Infantile Haemangioma.

Discussion:

Infantile haemangiomas are most benign vascular tumour of infancy, arise due to benign endothelial cell proliferation mostly in first two months of age(17), moreover first outcome of topical timolol solution was used in 4-month-old infant with superficial infantile hemangioma by Guo and Ni(18). Timolol is well tolerated, easy to administer and cost effective, topical timolol usually given in dose of 2 to 3 drops reduces the erythema of infantile haemangioma and thereby decreasing size of IH.

In our study we analyzed that infantile haemangiomas are more prevalent in females(60.7%)

which is consistent with other studies(7), while as in our study most cases having infantile hemangioma involve head and neck(47%) followed by trunk(33.3%) and lower extremities(19.7%) which has been reported by various studies(3)

In a study by Yu et al.(19), carried out study in 124 cases of IH, among these 101 cases with IH received topical timolol, while 23 were controls also photographic evaluation done to analyse changes in size and colour. regression in hemangiomas was seen in 57 (56%) patients after 4 months which is again in accordance with our study. Mechanism of action of timolol involves inhibition of growth factors and vasoconstriction responsible for

proliferative phase, while as Systemic beta-blockers (propranolol) also result in vasoconstriction with complication (20), although in contrast topical timolol is safe and effective with least adverse effects which is concurrent with our study. It has been reported that multiple hormonal factors, like epinephrine, catecholamines and vascular endothelial growth factors (VEGF) play role in progression and pathogenesis of hemangiomas (21) (Boscolo and Bischoff, 2009). β -blockers inhibiting various pathway signals like thrombospondin-1, protein kinase B, and hypoxia-inducible factor-1 (22) (Munabi et al., 2016; Lin et al., 2018; Xu et al., 2018). therefore topical beta blockers provide better substitute contrary to systemic beta blockers in treating superficial infantile haemangiomas due to minimal side effects.

It has been reported that regression of IH's by using topical 0.5% timolol maleate occurred before spontaneous regression (around 9-12 months) (24,26) while in our study, complete regression in 18 cases occurred upto 16 weeks and in 12 cases regression started around 8 weeks from treatment onset. Spontaneous regression of IH's in comparison with hemangiomas treated with timolol maleate 0.5%, morphological differences was observed in IH treated with topical timolol compared to spontaneous regression, as in IH treated with topical beta blockers endothelial cells regression with apoptosis was observed (25,26)

Topical timolol maleate (0.5%) treatment in superficial Infantile haemangiomas appears useful and safe treatment modality in patients of infantile haemangioma particularly up to 6 months of age.

Conclusion:

Topical timolol maleate (0.5%) is considerably effective and safe treatment in infantile haemangioma, therefore can be recommended for superficial and small infantile hemangiomas due to very less adverse effects. our study also provides supportive evidence and clinical experience of using topical timolol (0.5%) a for treating superficial infantile haemangiomas and thus appears to provide an ideal treatment for IH as reported by other studies.

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