

STUDY OF EFFECTIVENESS OF TOPICAL TIMOLOL MALEATE IN THE MANAGEMENT OF SUPERFICIAL INFANTILE HAEMANGIOMA

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ABSTRACT

BACKGROUND

The aim of the study is to evaluate the effectiveness of topical 0.5% timolol maleate solution for superficial infantile haemangioma (IH).

MATERIALS AND METHODS

This prospective study was carried out over a period of 4-years and included patients of IH. All patients were managed on out-patient basis. Parents were asked to apply 2 drops of 0.5% solution of timolol maleate eye drops over the entire haemangioma two times in a day. The total duration of treatment was 8 months. They were called for review on 15th day, then every two months for a total period of one year. Any side effect or recurrence were noted. The response was categorized into five groups: no response, controlled growth, partial response, good response and excellent response.

RESULTS

78 patients who satisfied inclusion and exclusion criteria were included in this study. All patients showed response to topical timolol application. Timolol application resulted in controlled growth in six patients (7.7%); partial response in seven (8.9%) patients; good response in 21 (26.9%) patients and excellent response in 44 (56.4%) patients. Complete regression was observed in 35 patients after completing the treatment. No patient showed any relapse in 6 months follow up after completion of treatment. Significant difference in the degree of response was noted between patients less than 6 months and more than 6 months. Also, the response rate in patients less than 2 months was significantly higher than that in older patients. None of the parents reported any adverse effects of the drug during treatment.

CONCLUSION

0.5% timolol maleate solution is an effective therapy option for infantile haemangioma without any major side effects and should be considered as a regular treatment.

KEYWORDS

Superficial Infantile Haemangioma, Topical Timolol Maleate.

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BACKGROUND

Infantile haemangioma (IH) are the most common benign vascular tumour in children affecting approximately 5% to 10% of children.¹⁻² The disease is often present at birth, although it may not be noticed until a few weeks later when the lesion begins its proliferative phase. During the first 9 months of age, the lesion grows rapidly, then stabilizing. Involution is complete in most children by 4 years of age. The majority of the lesions regress spontaneously, and do not require treatment. However, the degree and rate of involution of involution cannot be predicted. The lesions may

cause cosmetic disfigurement and morbidity. Also, they are usually a significant source of parental apprehension. Thus, IH warrants appropriate management for improving patient outcomes.³

Various modalities of treatment for haemangiomas has been described but most common include oral steroids and beta-blocker propranolol. However, they may be associated with systemic side effects. Topical corticosteroids are effective for superficial, small, and uncomplicated haemangiomas. But they may be associated with high nonresponse rate and skin hypopigmentation and atrophy.⁴ Oral propranolol, a non-selective beta blocker, has proven to be an effective alternative to corticosteroids, which have many potential side effects. Topical timolol is a promising alternative in the treatment of IHs since it has been reported to inhibit the growth and promote regression of superficial IH.⁵⁻⁸ It improves the therapeutic efficacy and reduce systemic adverse effects of IH. As it is more potent than propranolol concerns have been raised regarding systemic absorption and side effects.⁵

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Thus, this prospective study is aimed to evaluate the efficiency and side effects of topical 0.5% timolol maleate solution for superficial IH.

MATERIALS AND METHODS

This prospective study was carried out in Department of Paediatric Surgery, Government Medical College Nagpur and included patients of IH treated over 4-year period, from July 2014 to August 2018. Approval from hospital ethics committee was taken to conduct this study. Patients were enrolled after obtaining written, informed consent from the patient's parents/guardian. The diagnosis of IH was based on history and findings of examination. The typical history of IH about the appearance of lesion days or weeks after birth was noted. This delay between birth and growth phase was used as a diagnostic tool in determining the correct diagnosis of IH. Patients less than 12 months; cutaneous superficial IH diagnosed according to the Waner and Suen 1999 classification criteria⁹ were enrolled in the study. Patients with prior history of treatment, history and findings of regression were excluded from study. Children with respiratory problems, sinus bradycardia and second- or third-degree atrioventricular block were also excluded from the study.

All patients were managed on out-patient basis. Parents were asked to apply 2 drops of 0.5% solution of timolol maleate eye drops over the entire haemangioma two times in a day. The total duration of treatment was 8 months. The parents were asked to take photographs of the lesion before starting the therapy and then once every fortnight and were asked to note changes in tumour colour and size. They were also informed about the potential adverse effects, such as sleep changes, irritability, local itching and ulceration, and were told to report if any of such symptoms appear. They were called for review on 15th day, then every two months for a total period of one year. Any recurrence in the form of increase in size after stopping the treatment was also noted.

From history and on comparison with the initial photographs, the response was categorized into five groups: No response when the lesion continued to grow despite timolol application; controlled growth, i.e. the lesion stopped growing however did not show significant change in size, colour or texture; partial response when there was reduction up to 50% in size; and good response when tumour was reduced by 50 to 75% and excellent response when tumour reduced by >75%.

The Chi-squared test and Fisher's exact tests were used to compare the response rates. p values less than 0.05 were considered statistically significant. Statistical analysis was performed using Stata Software version 10.0.

RESULTS

A total of 83 patients attended outpatient department for management of IH. However, 78 patients who satisfied inclusion and exclusion criteria were included in this study. Patient related characteristics are given in Table 1. All these patients were given 0.5% timolol eye drops for topical application. At first follow up, after 15 days of the initiation

treatment, 73% of the lesions became softer and faded in colour. Table 2 depicts the response rate according to age of presentation. Figure 1 shows the clinical response of the patient. All patients showed response to topical timolol application. Timolol application resulted in controlled growth in six patients (7.7%); partial response in seven (8.9%) patients; good response in 21 (26.9%) patients and excellent response in 44 (56.4%) patients. Complete regression was observed in 35 patients after completing the treatment. No patient showed any relapse in 6 months follow up after completion of treatment. On sub group analysis, significant difference in the degree of response (controlled growth and partial response verses good and excellent response) was noted between patients less than 6-month and more than 6 months group ($P<0.05$). Also, the response rate in patients less than 2 months was significantly higher than that in older patients ($P<0.05$). None of the parents reported any adverse effects of the drug during treatment.

Patient Characteristics		
Sex (n)	Male	31
	Female	47
Age at initial treatment (in months)	0-2 months	23
	2-6 months	31
	>6 months	24
Tumour size (in mm×mm) (Mean ± SD)		58.49×43.43±39.23×24.67
Mean birth weight ± SD (in Kg)		2.74±1.28
Gestational age (in weeks) mean ± SD		36.45±2.86
IH location	Head and neck	36
	Extremities	18
	Trunk	24

Table 1. Clinical Characteristics of Patients

Response Rate	<2 Months (n=23)	2-6 Months (n=31)	>6 Months (n=24)	Total
Controlled growth	0	2	04	06
Partial response	0	02	05	07
Good Response	02	10	09	21
Excellent response	21	17	06	44
Complete Resolution (Subgroup of excellent response)	18	16	01	35

Table 2. Response of Topical Timolol in the Treatment of Superficial IH According to Age

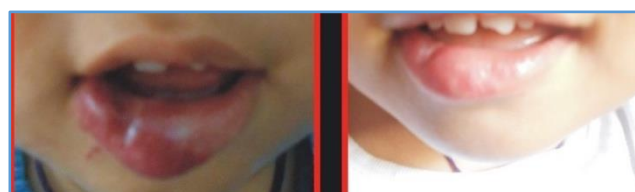


Figure 1

DISCUSSION

The majority of IHs proliferate, stabilize, and regress without the need for intervention beyond anticipatory guidance. The initial proliferative phase begins in the first 2 weeks of life, then followed by a plateau phase. The involution phase starts at after the first year and is continued until 4-6 years.¹⁰ However, in a significant minority, size or location may necessitate intervention to treat or prevent local disfigurement, functional impairment, or systemic complications.

Various modalities for treatment are available including oral and systemic steroids and β -blockers. Because of systemic side effects of oral drugs, local therapy is usually preferred. Topical corticosteroids are usually associated with high nonresponse rate and may result in skin hypopigmentation and atrophy.⁴ The finding that topical timolol application resulted in regression of IH led to a widespread enthusiasm for use of this agent in management of IH. The proposed therapeutic effects of β -blockers on IHs are vasoconstriction; decreased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) genes through down regulation of the RAF/mitogen-activated protein kinase pathway, and apoptosis of capillary endothelial cells.^{11,12}

Timolol maleate ophthalmic solution is available 0.5% strength. One drop of medication contains 0.25 mg of timolol maleate. The systemic bioavailability of 1 intraocular drop (0.05 mL) of timolol maleate 0.5% solution is variable but may be as high as 80%. There is very limited information regarding off-label safety and pharmacokinetic data when used on haemangioma-affected skin. The 8- to 10-fold increased potency of timolol maleate compared with that of propranolol raises concern for potential systemic toxicity from topical therapy. The onset of timolol's effect is reported to be more gradual and modest than that typically seen with systemic β -blockers. We favour using 2 drops of timolol application for two times a day regardless of IH size; instructing parents to massage the solution over the IH. In larger IHs, varying the site of timolol application within the IH was advised.

The first successful use of timolol solution was described for superficial haemangioma of the eyelid in a 4-month-old infant in 2010.¹³ Similar success was subsequently reported by many researchers.⁵⁻⁸ The findings of this study corroborates with the results of previous studies that topical timolol maleate is a promising and effective treatment modality for treatment of superficial IHs. Recently published meta-analysis quotes 91% resolution rate with topical timolol.¹⁴

In all of our subjects, topical timolol application was associated with growth arrest and a reduction in redness within the first 4 weeks of treatment. We graded the response in term of reduction in size of lesion. 83% lesions showed reduction by more than 50% of initial size while more than half of the lesions reduced by two-third of initial size. Complete resolution was seen in 45% of lesions. Our study substantiates the findings of previous studies that early intervention during the rapid proliferative phase (age

less than 2 months) may result in better and faster resolution of IHs. Xu et al found that the therapeutic response of children who started treatment with propranolol ointment between the ages of 0–3 versus 3–6 or 6–10 months had a statistically significant difference.¹⁵ Typically younger patients with superficial IHs have a greater likelihood of response to topical therapy. Nearly 80% of patients younger than 2 months at the initiation of therapy, showed complete resolution while only one patient who presented after six months had complete response.

The topical timolol appears to be a safe drug. Most of the studies have reported a very low incidence of side effects.⁴⁻⁸ Reported side effects include burning sensation, skin irritation, dizziness, wheeze or cough. Sleeping disturbance, was the only reported side effect noted in a large meta-analysis.¹⁴ We did not encounter any side effects in our study. There were no side-effects even on topical timolol application on mucosal surfaces. Although our study provides substantial data regarding the effectiveness and safety of timolol for IH therapy, the limitations of present study are small sample size, lack of control group, lack of standardized surveillance for heart rate and respiration.

CONCLUSION

0.5% timolol maleate solution is an effective therapy option for infantile haemangioma without any major side effects. It is more effective when started early in the natural history of disease and should be considered as a regular treatment.

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