Efficacy and safety of topical β blockers (0.5% timolol maleate eye drops) in the treatment of infantile haemangiomas

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Sri Lanka Journal of Dermatology, 2011, **15**, 40-44

Abstract

Background: Therapeutic options for infantile haemangiomas (IH) are limited. Recently, timolol maleate, a topical nonselective betablocker, has been reported as a potentially effective treatment for IH.

Objectives: To assess the efficacy and safety of topical blockers (0.5% timolol maleate eye drops in the treatment of infantile haemangiomas.

Methods: Study was carried out at the Dermatology Unit of the Lady Ridgeway Hospital for Children, Colombo. All Infants referred to the Dermatology Clinic, aged 2 months to 2 1/2 years who had uncomplicated haemangiomas of proliferative phase irrespective of the anatomical site were selected after the informed written consent. 0.5% timolol maleate eye drops were applied twice a day as the treatment. Two investigators independently analyzed the response to treatment by comparing digital photographs at baseline vs 4 weekly for one year or up to resolution.

Results: 40 subjects were identified. Female preponderance was seen (70%). Cox proportional hazard regression reveled group of patients who were started treating during the 1st year of life show better outcome. (treatment median 5 months) (p value 0.002). No side effect were reported.

Conclusions: Topical β-blocker (timolol 0.5% ophthalmic solution) administration provides a safe and effective alternative for treating infantile haemangiomas. Best time for timolol treatment were the IH is in it's early proliferative phase.

Introduction

Infantile haemangiomas (IH) are among the most common, benign vascular tumours of infancy with an estimated prevalence of 4-5% of the population with female preponderance. IH are not found at birth but become evident within the first few weeks of life. Most of the haemangiomas undergo spontaneous involution, with only small propotion requires intervention. Eighty percent of hemangioma grow during the early proliferative stage, around three months of age, undergo involution which may not be completed. Most haemangioma growth occurs before five months. Completed involution occurs at an estimated minimum rate of 10% per year, approximately 50 % of haemangiomas have involuted by age five years, 70% by age seven, and 90% by age nine[1,5].

Beta blockers (propanalol), systemic corticosteroids (prednisolone) are the common pharmacological treatment options for years. Cryotherapy and plastic surgery are the other interventional options in Sri Lanka. Use of topical timolol (a non selective beta blocker) has emerged as a drug with low systemic side effect profile[2,4]. Standard treatment regime and guidelines for using topical timolol for IH is currently not available.

Objectives

General objectives

To assess the efficacy and safety of topical blockers (0.5% timolol maleate eye drops) in the treatment of infantile haemangiomas.

Specific objectives

1. To recommend 0.5% timolol eye drops as a standard therapy for infantile haemangiomas in Sri Lanka.
2. To recommend standard treatment regime for timolol in treating infantile haemangiomas.
3. To describe the side effects, if any of timolol therapy in treating infantile haemangiomas.

Methodology

Study design: Interventional study.

Study setting: Dermatology Unit, Lady Ridgeway Hospital for Children, Colombo.

Study period: From 1st March 2011 to 31st March 2012.

Sample size: According to the multicenter study

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which was conducted in Canada in 2010[2] sample size of 40 was adequate for the analysis.

Sampling method: Convenient sampling.

Inclusion criteria: Infants aged 2 months to 2 1/2 years who has uncomplicated haemangiomas of proliferative phase irrespective of the anatomical site were registered to the study after informed written consent was obtained from the parents or guardian.

Study intervention: 0.5% timolol maleate eye drops applied twice a day as the treatment.

Method of data collection: Two investigators independently analyzed the response to treatment by comparing digital photographs at baseline vs 4 weekly for one year or up to resolution and it will be recorded in the patients' follow up sheet.

Method of data analysis: Data was analyzed after entering in to the electronic format (spreadsheet) and it was analyzed by using SPSS (ver. 18). Descriptive statistics and survival/end point analysis methods (Kaplan-Meier and Cox proportional hazard regression) were used to analyze the covariates. Probability value (p value) of 0.05 considered as the cut off level for significance.

Results

Forty subjects were identified. There was a female preponderance (28, 70%). The median age for starting treatment was 10 months with inter quartile range (IQR) was 5-17 months (Mean 11.3 months ± 7.399 months). Head and neck area was the common anatomical area (16, 40%) followed by trunk (7, 17.5%), extremities (8, 20%) and perineum (6, 15%). Twenty six patients (26, 65%) had a single lesion. Median duration of treatment until cure of 32 subjects was 5 months with IQR 4 - 6 months (Mean 5.72 months ± 1.78 months). Better cure rates were observed than the natural history (Figure 1).

Kaplan-Meier regression analysis shows significant association with 2 factors (Table 1) independently. Further analysis with Cox proportional hazard regression which was adjusted for all the covariates shows only the significant (p-value <0.001) with treatment initiation time category (95% confidant interval for the estimator does not include 1) (Table 2). That concludes the fact that starting treatment before one year provides statistically significant improvement of IH (Figure 2). The other factors showed significance in individual analysis has lost their significance after adjusted for all the covariates in a single model.

No side effects such as skin-related adverse events like local burning, stinging, or irritant reactions were noted in any of the subjects. Rebound growth of IH after treatment discontinuation at 3-6 months was not observed.

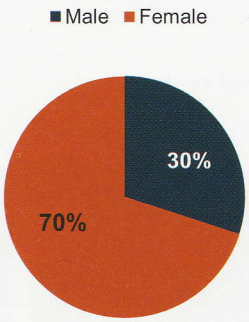

Figure 1. *Sex distribution.*

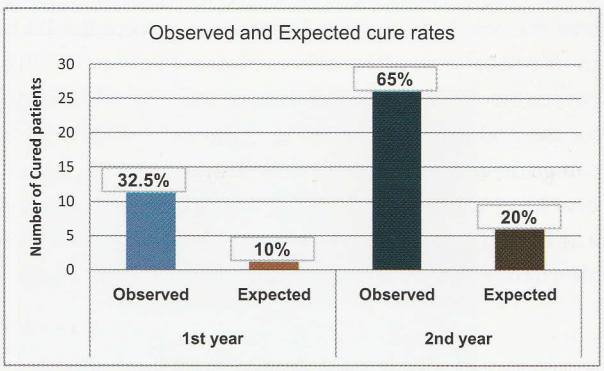

Figure 2. *Observed and expected cure rates.*

Table 1. Significant levels with Kaplan-Meier regression

Factor	*Significance*
1. Sex	0.782
2. Number of lesions (single/ more than one)	0.041
3. Site (head and neck/trunk/ extremities/perineal/other) - between perineal and other only	0.021
4. Treatment initiating age (within one year/within 2nd year)	<0.001

Table 2. Cox propotional hazards regression model parameters

				95.0% CI for Exp (B)	
	df	*Sig.*	*Exp (B)*	*Lower*	*Upper*
Number of lesions	1	.129	2.033	.814	5.080
sex	1	.806	1.126	.436	2.908
site	4	.739			
site (1) - head and neck	1	.311	2.294	.460	11.431
site (2) - trunk	1	.437	2.151	.312	14.819
site (3) - extremties	1	.687	1.399	.273	7.179
site (4) - perineal	1	.341	2.281	.418	12.453
Age at start of treatment	1	.002	4.822	1.769	13.146

Discussion

Most of our patients presented late for treatment with a median age of 10 months. The treatment was effective in 32 (80%) patients out of 40. This study demonstrates early intervention (before age of 1 year) was the best time for timolol treatment were the IH is in it's early proliferative phase (Table 3: 99th percentile for 1st year group is 6 months where and for the 2nd year is 10 months) (Figure 3: Box plot for 2 categories). These results also suggest that topical β-blocker (timolol 0.5% ophthalmic solution) administration provides a safe and effective alternative for treating infantile haemangiomas.

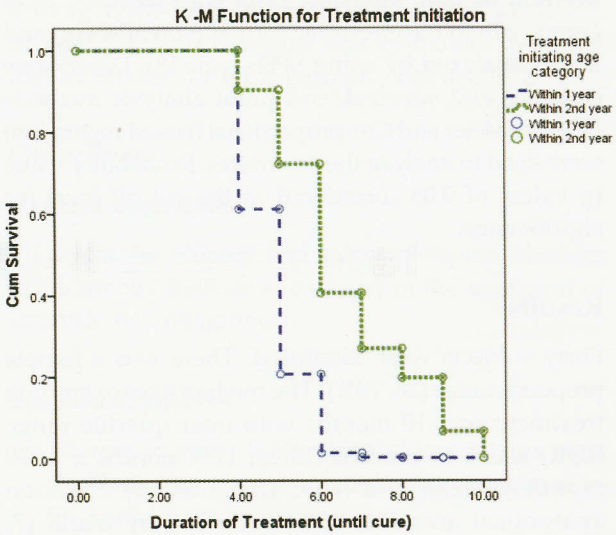

Figure 3. *Kaplan-Meier function for treatment initiation.*

Table 3. Statistics two treatment initiation groups

Statistic	*Within 1st year*	*Within 2nd year*
Mean	4.74	7.15
Standard deviation	0.81	1.86
Median	5.00	7.00
Percentile 25	4.00	6.00
Percentile 75	5.00	9.00
Percentile 99	6.00	10.00
Minimum	4.00	5.00
Maximum	6.00	10.00

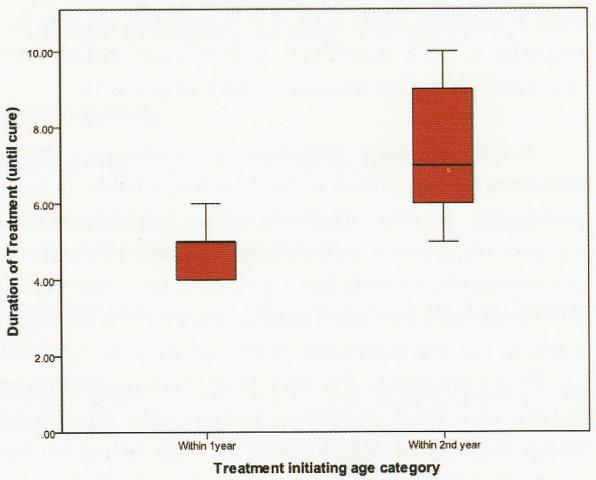

Figure 4. *Box and whisker plots for duration of treatment until cure and treatment initiation.*

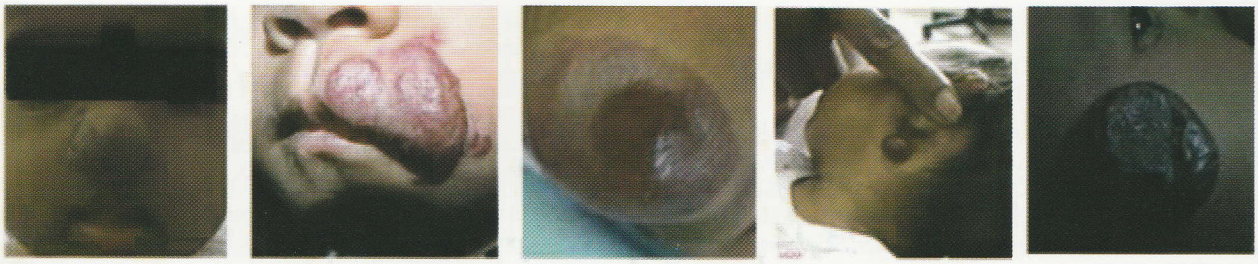

Image 1 – Initial visit

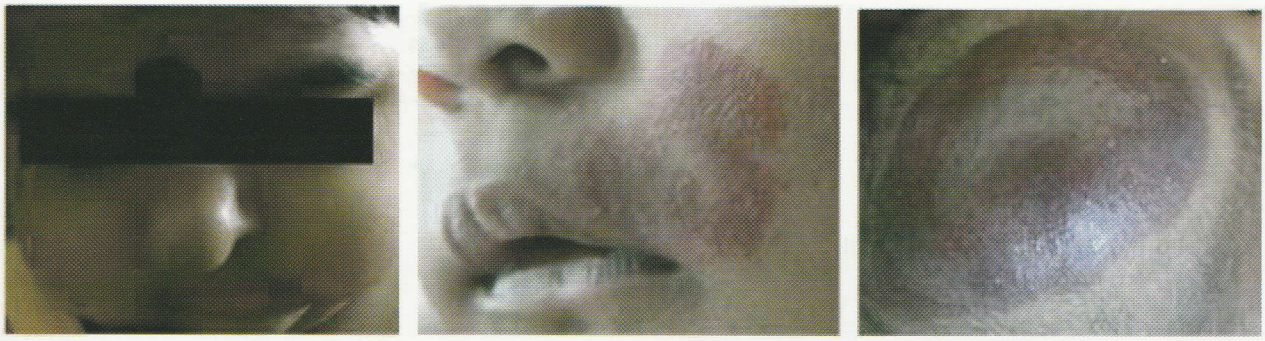

Image 2 – Responded patients

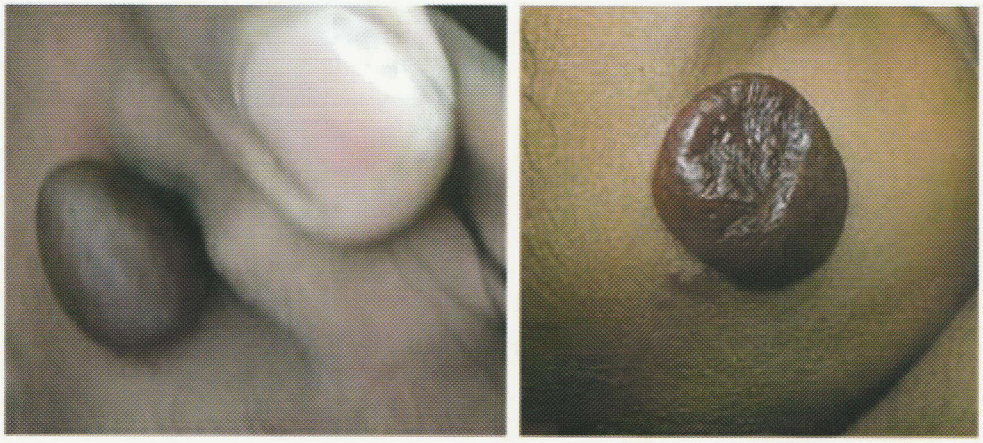

Image 3 – Poorly responded patients

The major advantages of topical timolol are ready availability, cost, ease of administration, and minimal risk of drug-related adverse events, especially when applied to the face and in particular the periorbital area.

Several case reports have noted the association between drug-related wheezing, bradycardia, and respiratory depression, especially in infants and children treated with ocular timolol solutions for longer period.

Ophthalmic timolol gel has been shown to have less or insignificant systemic bioavailability than timolol ophthalmic solution[3,6]. This aspect was not assessed in this study.

The use of tropical timolol may require further investigations. We can recommend the use of topical timolol in the early proliferative phase to obtain a better outcome.

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