Original Article

Oral versus topical propranolol in infantile hemangiomas

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Objective: To determine the therapeutic response rate of oral and topical propranolol in infantile hemangiomas (IH).

Methodology: A sample size of 60 patients was calculated using WHO calculator. Non probability consecutive sampling was used. Ethical approval and consent forms were taken. Patients were randomly divided into two groups using lottery method. Group A was given oral propranolol and Group B was given topical timolol. Both groups were followed for 3 months for Visual analogue scale of therapeutic response rate. Data was analyzed using SPSS version 24. Chi-square test was applied. P value ≤0.05 was considered significant.

Results: Total 60 infantile hemangioma patients were included in study. Mean age of patients was 5.4months±1.9SD. There were 32(53.3%) male and 28(46.7%) female. Therapeutic response rate was higher in topical timolol as compare to oral propranolol (p=0.003). Adverse effects were significantly higher in oral propranolol group as compare to topical timolol (p=0.000).

Conclusion: Topical timolol is safe and effective treatment in infantile hemangiomas as compare to oral propranolol. Topical timolol poses less risk of inducing adverse effects among infants. Therefore, topical propranolol is recommended for small and superficial infantile hemangiomas. (Rawal Med J 202;45:611-615).

Keywords: Infantile hemangiomas, propranolol, response rate.

INTRODUCTION

Infantile hemangiomas (IH) are most common benign lesions that lead to orbital and eyelid tumors in childhood.[1] Incidence of infantile hemangiomas is 3-10% in developing countries.[2] Caucasians are more prone to have infantile hemangiomas as compare to blacks, Taiwanese and Japanese (12%, 1.4%, 0.2% and 1.7% respectively).[3] Risk factors associated with IH are prematurity, female gender, multiple gestations, low birth weight, Caucasian ethnicity and advanced maternal age.[4] The infantile hemangiomas significance depends upon age, size and location of lesion. Most common sites for infantile hemangiomas are head and neck during childhood.[5]

According to clinical presentations lesions are divided into three main subtypes depending upon depth of involvement. Superficial lesions are usually red bright papules that may have bumpy or flat appearance. Deeper lesions have blue or purple coloration and cause variable changes in skin. Third subtype components of both deep and superficial lesion in infantile hemangiomas. Clinical course of infantile hemangioma is divided into six stages including nascent, early proliferative, late proliferative, plateau, involution and abortive stage.[6] Amblyopia is most common complication of infantile hemangioma, when lesion area is greater than 1cm. Infantile hemangioma in eyelid results in induced astigmatism and occlusion of visual axis leading towards anisometropic amblyopia and deprivation amblyopia.

Orbital lesions in infantile hemangioma attribute towards strabismus, exposure keratopathy, proptosis and compressive optic neuropathy. Out of all patients, 40-60% patients are affected by amblyopia and 40-80% leaves permanent residua after tumor involution.[7] Management of infantile hemangioma includes medical therapy (use of steroids and interferon-alpha), vincristine, laser therapy and surgical therapy. New trends in treatment of IH (use of beta-blockers) were seen after discovery of propranolol efficacy in 2008. Propranolol is used as topical and orally in both forms for treatment of IH. A study explained mechanism of action of propranolol tumor growth inhibition with propranolol in three following ways including i) vasoconstriction, ii) inhibition of angiogenesis, iii) induction of capillary endothelial cells apoptosis.[8]

Literature reported that oral and topical timolol both had significant satisfactory results. They reported a response rate of 97% with oral and 96.4% with topical timolol. However, patients treated with oral timolol were more prone to have adverse effects as compare to topical timolol (3.9% & 0% respectively).[9] Oral propranolol showed clinical response in 94.3% patients of infantile hemangioma.[10] Another study reported that oral propranolol is effective in reducing periocular lesions among 66.6% patients with more than 50% reduction in lesion size.[11] Limited data is available on infantile hemangiomas in Pakistan. Present study aims to determine therapeutic response rate of oral and topical propranolol in infantile hemangiomas.

METHODOLOGY

This randomized controlled trial (RCT) was conducted at pediatric department, Izzat Ali Shah Hospital, Wah Cantt. Study duration was six months from June to November 2018. Ethical approval was taken from ethical review board of the hospital. A sample size of 60 patients was calculated (1:1) with 95% confidence interval, 5% significance level, p1 84.2% and p2 5.3%[12] using WHO calculator. Non probability consecutive sampling was used for patient's selection. Patients with age ≤1 years, both genders and diagnosed with infantile hemangiomas (IH). Exclusion criteria were based upon patients with beta blockers contraindications (bronchial asthma, hypoglycemia, heart failure, heart block, sinus bradycardia, and hypotension) and allergy to beta blockers. Consent forms were signed by either of the parents (mother, father or any other legal guardian in the absence of parents) in the presence of researcher.

Patients were undergone detailed history, clinical examination, ultrasound investigation, blood sugar and blood pressure measurement and echocardiography. Patients were randomly divided into two groups using lottery methods. Group A was given oral propranolol 2 mg/kg/day (divided 2 times a day) while Group B was given topical timolol maleate gel 0.5% (three times daily) applied on surface of lesion. Patients were followed after 3 months. Therapeutic response was graded visual analog scale (VAS). They were classified as excellent (90-100 scores), good (51-90scores), fair (1-50 scores), poor (-100 to 0 scores). **Statistical Analysis:** Data were analyzed using SPSS version 24. Mean and standard deviation was calculated for descriptive statistics. Frequency and percentage were calculated for qualitative variables. Chi-squares test was applied. p value ≤0.05 was considered significant.

RESULTS

Among all the patients treated with oral propranolol 30(50%), therapeutic response rate was excellent in 5(8.3%), good in 7(11.7%), fair in 9(15%) and poor in 9(15%). Similarly among all the patients treated with topical timolol 30(50%), therapeutic response rate was excellent in 13(21.7%), good in 11(18.3%), fair in 6(10%) and poor in 0(0%) patients (p=0.003) as shown in Table 1. Adverse effects were significantly higher in oral propranolol group with high frequency of strabismus following, optic neuropathy, others, proptosis and exposure keratopathy (15%, 13.3%, 11.7%, 10% and 1.7% respectively) as compare to topical timolol (p=0.000) as shown in Figure 1.

Table 1. Therapeutic response rate in oral versus topical propranolol in IH patients.

Therapeutic response rate	Interventional groups		Total	p value
	Oral Propranolol	Topical timolol		
Excellent	5(8.3%)	13(21.7%)	18(30%)	0.003
Good	7(11.7%)	11(18.3%)	18(30%)	
Fair	9(15%)	6(10%)	15(25%)	
Poor	9(15%)	0(0%)	9(15%)	
Total	30(50%)	30(50%)	60(100%)	

Figure 1. Comparison of Adverse effects in both interventional groups.

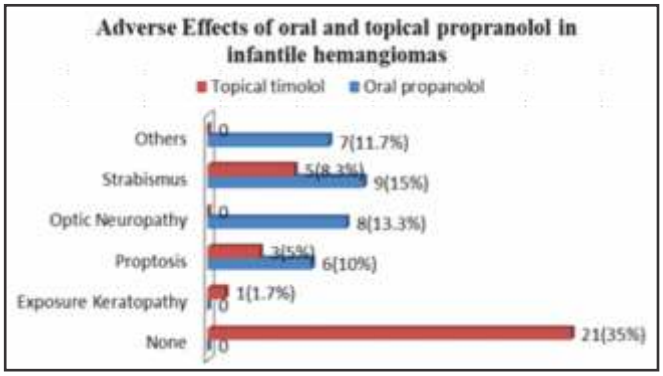

Figure 2. Comparison of infantile hemangiomas on arm before (A) and after (B) treatment.

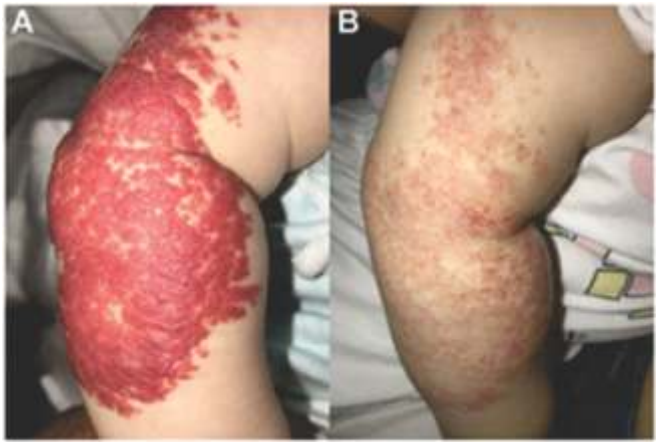

Table 2. Comparison of independent variables in both interventional groups.

Age	Interventional groups		Total	p value
	Group A Oral Propranolol	Group B Topical timolol		
1st day – 6 months	27(45%)	15(25%)	42(70%)	0.002
7-12 months	3(5%)	15(25%)	18(30%)	
Gender				
Male	14(23.3%)	18(30%)	32(53.3%)	0.438
Female	16(26.7%)	12(20%)	28(46.7%)	
Location				
Head and neck	20(33.3%)	27(45%)	47(78.3%)	0.06
Extremities	7(11.7%)	3(5%)	10(16.7%)	
Trunck	3(5%)	0(0%)	3(5%)	
Lesion size				
0-5 cm^2	15(25%)	16(26.7%)	31(51.7%)	1.00
>5cm^2	15(25%)	14(23.3%)	29(48.3%)	
Total	30(50%)	30(50%)	60(100%)	

Among all the patients in oral propranolol group 30(50%), 27(45%) were in age group 1st day to 6 months and 3(5%) were in age group 7-12 months. Among all those in topical timolol group 30(50%), 15(25%) were in age group 1st day to 6 months and 15(25%) were in age group 7-12 months (p=0.002). Gender, location of lesion, size of lesion were insignificantly associated with both interventional group (p=0.438, p= 0.06, p=1.00) as shown in Table 2.

DISCUSSION

Infantile hemangioma (IH) is one of very common vascular benign tumor of infancy, worldwide.[13] In present study; total 60 infantile hemangiomas patients were included in study. Mean age of patients was 5.4months±-1.9SD. Location of lesion was head and neck in 47(78.3%), extremities in 10(16.7%) and trunks in 3(5%) patients. Puttgen et al reported that neck and head is most common site for infantile hemangiomas (57%).[14] Moreover, Leaute-Labreze et al reported that frequency of hemangiomas was higher in head and neck as compare to other sites (55% vs 2%, p=0.02).[15]

In present study, lesion size was 0-5 cm^2 in 31(51.7%) patients and >5cm^2 in 29(48.3%) patients. Wedgeworth et al reported that majority of patients with infantile hemangiomas had mean lesion size 4.5±1.5cm.[16] Another similar study reported that lesion size is significant factor in treatment of infantile hemangiomas (p=0.00).[17] In present study, therapeutic response rate was higher in topical timolol as compare to oral propranolol (p=0.003). Moyakine et al reported that there is no significant difference in response rate of topical and oral propranolol (p=0.32).[18] Another similar study reported that efficacy of topical timolol maleate is higher as compare to oral propranolol (p=0.01).[19] Storch et al reported that topical propranolol is more effective and safe in small and superficial infantile hemangioma as compare to oral propranolol (p=0.000).[20]

In present study, adverse effects were significantly higher in oral propranolol group with high frequency of strabismus following, optic neuropathy, others, proptosis and exposure keratopathy (15%, 13.3%, 11.7%, 10% and 1.7% respectively) as compare to topical timolol (p=0.000). Painter et al reported that patients treated with oral propranolol were more prone to have systemic complication as compare to topical propranolol (RR:1.2, 95% C.I, p=0.00).[22] Gong et al reported that there is no significant difference in local complications of oral and topical propranolol (p=0.05).[23]

In present study, gender, location of lesion, size of lesion were insignificantly associated with both interventional group (p=0.438, p= 0.06, p=1.00). Novoa et al reported that female gender, age, location of lesion are dependent predictors of infantile hemangioma (p=0.000).[24] However, Xu et

al reported that patients with young age and with lesion at neck and head are more responsive towards topical propranolol as compare to oral propranolol (p=0.02).Single center study with a small sample size limits generalizability of our study.

CONCLUSION

Topical timolol is safe and effective treatment in infantile hemangiomas as compared to oral propranolol. Topical timolol poses less risk of inducing adverse effects among infants. Therefore, topical propranolol is recommended for small and superficial infantile hemangiomas. Further research is needed on details efficacy of oral and topical propranolol for all types of infantile hemangiomas including with and without ulceration.

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Conflict of Interest: None declared
Rec. Date: Feb 19, 2020 Revision Rec. Date: Jun 4, 2020 Accept Date: Jun 16, 2020

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