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ORIGINAL ARTICLE

COMPARISON OF OUTCOME OF OUTPATIENT TOPICAL TIMOLOL VS. ORAL PROPRANOLOL IN MANAGEMENT OF INFANTILE HEMANGIOMA: A SINGLE CENTER EXPERIENCE – A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: There is some debate about whether oral propranolol or topical timolol are more effective for treating infantile hemangioma, and only a few studies are available in the literature. The project aimed to compare efficacy and safety of topical timolol vs. oral propranolol in the management of superficial infantile hemangiomas in outpatients in terms of size reduction, color change and duration of treatment.

Materials & Methods: This randomized controlled trial was conducted at the Department of Pediatric Surgery, Lady Reading Hospital, Peshawar after IRB approval. Sixty patients with superficial infantile hemangioma were selected and were randomized into two groups, 30 in each group using the balloting method; Group-A (taking propranolol) and Group-B (taking topical timolol). The propranolol was split into two doses and taken within half an hour after each meal. Applying timolol maleate 0.5% hydro gel topically three times a day was the standard course of action. Visual analogue scale (VAS) scores, color shifts, and treatment duration were used to assess the success of the therapy. Cosmetic improvement was used to assign a value on the VAS (from -100 to 100). Therapy responses were ranked as outstanding (90– 100), good (51–90), fair (1–50), or poor (100–0). All the data were entered in SPSS version 24 and analyzed.

Results: There was no significant difference for therapeutic response (Excellent therapeutic response: Propranolol: 42.5% vs. Topical Timolol: 45%, p-value=0.624) and adverse effects (p-value=0.112) in treatment groups.

Conclusion: Results of this study demonstrate that topical timolol and oral propranolol are equally effective for treating superficial infantile hemangiomas in terms of size reduction, color change, duration of treatment, efficacy and adverse effects.

KEY WORDS: Infantile hemangioma; Propranolol; Timolol.

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INTRODUCTION

Infantile hemangiomas (IHs), affecting up to 5% of infants are the mainly common benign vascular tumors in newborns. These lesions are more frequent in girls, twins' babies, and preterm infants.[1] These IHs most of the times are small and self-resolving; on the other hand, complex IHs with associated bleeding or infection may impair vital structures functions and needs attention.[2] The proliferative phase of a disease normally begins around 3-4 weeks of age and reaches its peak around 6-7 months of age due to an aberrant proliferation of endothelial cells of the capillary vessels.[2] After this time, the tumor rarely shrinks on its own, though it sometimes changes color.[3] Main diagnostic tools for diagnosing IHS are detailed history and clinical examination. Extracutaneous and cutaneous hemangiomas can be characterized by means of advanced imaging examinations like Doppler ultrasonography and magnetic resonance imaging (MRI). In addition to identifying IHs, MRI can distinguish them from other

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high-flow vascular lesions such AV malformations.[4]

A nonselective beta-blocker called propranolol has recently gained popularity as a systemic therapy option in place of corticosteroids. In order to treat IHs, propranolol constricts blood vessels and reduces the 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 induces death of capillary endothelial cells.[4] Evidence is mounting in support of using oral propranolol for hemangiomas as a first treatment option.[5,6] Systemic propranolol's safety is still up for debate, as it has been linked to serious side effects in several studies, including bronchial asthma, low blood pressure, high potassium levels, and low blood sugar.[7,8] According to a small number of investigations, Topical propranolol or timolol has been shown to be a useful and safe alternative to oral propranolol. Timolol, a nonselective beta-blocker like propranolol, is offered in a topical gel formulation for the treatment of glaucoma.[9] A European expert panel concluded in 2015 that topical beta-blockers may substitute oral steroids as the first-line therapy for superficial and small haemangiomas.[10]

Research has shown that the nonselective-blocker timolol maleate,0.5% gel is a useful and secures treatment for IHs. Those patients who were managed with prolonged duration responded well to timolol, according to another study. IHs may respond more favorably to treatment if it is administered during the early proliferative period (ages 1–6 months). This data also supports the use of 0.5% timolol maleate gel topically as another option to systemic propranolol in the treatment of infantile hemangioma.[11,12] Timolol was found to be a secure, moderately efficient treatment in one trial, with the best response seen in smaller, thinner His before treatment. Timolol may be advised for many people as an alternative to systemic blockers.[13] However, topical -blockers are not acceptable for recommendation as a routine therapy due to a lack of evidence proving their efficacy and safety in treating haemangiomas.[14] In the current study, we examined and followed patients taking either oral or topical treatment for the management of hemangioma. On reviewing the literature, there is controversy regarding the efficacy of topical timolol and oral propranolol in the treatment of superficial HIS.[9] Also, there are few studies available in the literature and no study available in local setup to the best of our knowledge.

MATERIALS AND METHODS

This randomized controlled trial was done at the Department of Pediatric Surgery, Lady Reading Hospital. Inclusion criteria include Patients presented in the outdoor department with superficial infantile hemangioma with no previous treatment, cutaneous hemangiomas were incorporated in the study. Exclusion criteria were those patients with deep IHs, or any prior contraindication for use of Beta-blockers, and those with ulceration. Before conducting the study, approval from the institutional review board was taken. Informed written consent was obtained from each patient for inclusion in the study. A purposive nonprobability sampling technique was used for patient selection, and a total of 60 patients were divided into two groups based on the balloting method.

- Group A taking propranolol
- Group B taking Timolol

A structured Performa was used to collect all the data after consent from the patients. There were 30 people in each study group. Patients' sexes, ages, locations of hemangiomas and prior therapies, as well as the patients' ages at the commencement of treatment, the length of treatment, any complications that arose, and any side effects that were experienced were recorded before treatment began. After determining each infant's cardiac status as a routine protocol at our unit, doctors at an outpatient clinic treated their IH with either medication after randomization. For group A taking oral treatment, propranolol was started at a dose of 0.3-2.0 mg/kg per day in 2 divided doses taken within half hours after meals. For group B, timolol maleate 0.5% hydro gel will be applied topically three times daily. Follow-up was done after every 4 weeks and carried out until resolution of symptoms. Care givers were told to stop giving the medicine to their patients if they had significant side effects such coughing, dyspnea, vomiting, or diarrhea. The VAS, a colour shift, and the length of treatment were all used to assess the effectiveness of the therapy. A VAS score, which can go from a negative value of 100 (indicating a doubling-up of the mass and area of the IH) to a positive value of 100(showing the entire resolution), was used for Changes in cosmetic appearance. Therapeutic responses were ranked as excellent (VAS score of 90–100), good (VAS score of 61-90), fair (VAS score of 31-50), or bad (VAS score of100-0). SPSS Version 24 was used to examine all of the data. P-value$<$0.05 was considered statistically significant.

RESULTS

Total of 60 patients with infantile hemangioma were received in the outpatient department. The Mean age of patients in Propranolol and Topical Timolol was 5.66$\pm$1.71 and 5.28$\pm$1.60 months respectively. Male patients were higher in number as compared to female patients. In propranolol group 20(67%) patients were male and 10(33%) were female while in topical timolol group 21(69%) patients were male and 9(31%) were female. In Propranolol group 13(43.5%) patients had lesion on head, 6(20%) on neck, 7(23%) on extremities and 4(13.5%) on trunk. In Topical Timolol group 12(39%) patients had lesion on head, 7(23.5%) on neck, 5(17%) on extremities and 6(20.5%) on trunk. The mean duration of treatment in both treatment groups ranges between 3-4 months. Nevertheless, in the Propranolol group, the average time on medication was 6.95$\pm$3.53month and the typical course of treatment for topically applied timolol was 6.45$\pm$3.88.

Table 1: Therapeutic response in study groups

	Propranolol	Topical Timolol	Total
Excellent	11(42.5%)	13(45%)	24
Good	6(18%)	7(23%)	13
Fair	7(21.5%)	6(21.5%)	13
Poor	6(18%)	4(10.5%)	10
Total	30	30	60
p-value	0.624		

Table 2: Adverse effect in study groups

	Propranolol	Topical Timolol	Total
Restless sleep	2(6%)	1(3.5%)	3
Diarrhea	1(3%)	0(0%)	1
Irritability	2(6%)	3(9%)	5
Vomiting	1(3%)	1(3.5%)	2
No side effects	24(82%)	25(86%)	49
Total	30	30	60
p-value	0.112		

The therapeutic response showed no significant difference between study groups. Excellent therapeutic response was 42.5% in Propranolol and 45% in Topical Timolol group. Whereas 18% of patients in propranolol and 10.5% of patients in topical Timolol group had poor therapeutic response i.e. p-value=0.624.

No significant difference was seen for adverse effects between the treatment groups i.e. p-value=0.112.

DISCUSSION

For the management of infantile hemangioma, many treatment options are available nowadays including oral, topical, intralesional and laser therapy, due to which wait is not advisable for its spontaneous resolution. Due to shortage of comparative studies, it always remains a debate to select a best treatment strategy in terms of effectiveness and with decrease adverse effects. In this study, the efficacy and safety of oral propranolol vs. Topical timolol was examined. Regarding the demographics of the patients, in our study there was no statistical difference in both groups and the results are consistent with those reported in literature.[15] By inducing vasoconstriction and angiogenesis inhibition, Propranolol suppress the growth of IHS.[16] Satisfactory therapeutic response could be achieved by using a propranolol dosage of 2-3mg/kg/day according to current studies. Furthermore, in the management of obstructive and ulcerated lesions, propranolol also remained to be a good choice. In our study, we advised propranolol to group A with dosage at0.3 -2 mg/kg per day to the patients, with a successful response rate of 82%, which is consistent with the results by Léauté-Labrèze et al.[17] These outcomes added additional support to the superior effects of propranolol for managing IHs. Regarding topical drug therapy, various formulations are available such as timolol 0.5 % gel forming solution. In our study, we applied topical timolol maleate 0.5% hydro gel to group B for managing IHs and revealed that acceptable clinical responses with mild side effects could be attained by using topical treatment as reported in the literature.[18] An Indian study recently reported that with using Topical Timolol for Infantile Hemangiomas resulted in 60% excellent results followed by 20% very good results and 15% good results which are almost consistent with our study.[19] Both β-blockers oral propranolol and topical timolol, which may control the growth of IHs in an analogous manner. Yet a small number of studies were done to evaluate the therapeutic effects of oral propranolol and topical timolol. In our study, results showed no significant difference for therapeutic response (Excellent therapeutic response: Propranolol: 42.5% vs. Topical Timolol: 45%, p-value=0.624) and adverse effects (p-value=0.112) in treatment groups which are Consistent with those as reported in literature, and both treatments can be adopted for superficial IHs.[9]Regarding adverse effects in both groups, sleep disturbances and poor feeding were seen in 5% of the infants which are almost same as reported by our study.[19] As such, all the studies on timolol conducted so far are not standardized and use different scoring systems to evaluate the response, and moreover, most of the studies are conducted with small sample sizes. One should not forget that the use of timolol to treat infantile hemangiomas is still an off-label use, the efficacy and safety of which is still under trials. Although timolol is effective in reducing the size of infantile hemangiomas and facilitates their early regression, long-term Studies need to be conducted to evaluate its safety in infants, especially the risk of systemic absorption.[19]

In the first instance, oral propranolol is prescribed for IHs. As more and more clinical trials of propranolol and related beta-blocker treatments are conducted, there are promising possibilities for its use in the treatment of this disease. The therapy of IHs has a wide variety of potential options. Propranolol medication and adverse effects, as well as emergency contacts, should be communicated to parents in writing. Propranolol should be given with feeds and doses should be skipped on the occasion of reduced oral intake, gastroenteritis, or chest infections. Dosage intervals should be set at least 8 hours apart.[20,21]

CONCLUSION

Results of this study demonstrate that both oral propranolol and topical timolol are equally effective for treating superficial infantile hemangiomas in terms of size reduction, duration of treatment, color change, efficacy and adverse effects.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	MR, MSS
Acquisition, Analysis or Interpretation of Data:	MR, MSS, JA, KS, SG
Manuscript Writing & Approval:	MR, MSS, JA, KS, SG

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.