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Original Research Article

Propranolol in the Management of Infantile Periocular Haemangiomas and A Comprehensive Evaluation of Ultrasound and Colour Doppler Imaging: A Prospective Study

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Abstract:

Background: Infantile periocular haemangiomas, the most common tumors in the orbit of children, often pose challenges in pediatric ophthalmology due to potential visual complications. This study explores the efficacy of propranolol in managing these vascular lesions, presenting a prospective study involving 5 patients.

Objectives: The aim is to evaluate changes in lesion size, refractive errors, and visual compromise while considering the safety and clinical relevance of propranolol as a therapeutic modality.

Methodology: Fifteen pediatric patients with infantile perioocular haemangiomas were enrolled in this prospective study and case series. Propranolol treatment was administered at a dose of 2 mg/kg/day. Comprehensive assessments included vision, refractive error, lesion characteristics, and monitoring for potential complications. Data were analyzed through t-tests to evaluate changes in lesion size and astigmatism.

Results: Propranolol treatment demonstrated positive outcomes across all patients. Lesion size reduction ranged from 54% to 96%, accompanied by improvements in refractive errors. Visual compromise, primarily astigmatism, diminished in patients with pre-existing issues. No significant complications were noted during the treatment period.

Conclusion: The results underscore the potential efficacy and safety of propranolol in managing infantile periocular haemangiomas. Reductions in lesion size, improvement in refractive errors, and resolution of visual compromise highlight the multifaceted impact of propranolol in this pediatric population. Ultrasound and CDI have emerged as valuable and accessible tools for diagnosing orbital lesions in the pediatric population Further research with larger cohorts and extended follow-up is essential for establishing propranolol as a standard approach in the management of these vascular lesions.

Keywords: Infantile periocular Haemangiomas, Propranolol, Pediatric Ophthalmology, Vascular Lesions, Refractive Errors, Visual Compromise.

Introduction

Infantile haemangiomas, the most prevalent tumors of the orbit in children, present a unique challenge in pediatric ophthalmology due to their potential impact on vision and ocular health.

Characterized as benign vascular lesions, these tumors typically manifest within the first month of life, undergo a phase of rapid growth until approximately 6 months of age, followed by a stabilization period, and eventually exhibit spontaneous involution over ensuing years.[1,2] In the periorbital region, infantile periocular haemangiomas may lead to vision deprivation, astigmatism, and strabismus, underscoring the importance of timely intervention to mitigate potential long-term visual sequelae.[3,4]

Historically, treatment options for infantile periocular haemangiomas have encompassed a spectrum of interventions, ranging from pharmacological agents such as steroids, alpha-interferon, vincristine, and cyclophosphamide, to procedural approaches like

lasers, embolization, and surgical excision.[5,6]While effective, these modalities pose inherent risks, particularly in the pediatric population, necessitating a cautious approach.

In recent years, a notable shift in the management paradigm has emerged with the successful utilization of propranolol, a non-selective beta-adrenergic antagonist, as a relatively safe and efficacious treatment for infantile periocular haemangiomas.[7] Propranolol's mechanism of action in inducing vasoconstriction and promoting apoptosis of endothelial cells has shown promise in halting the progression of these vascular lesions.[8–10]

The diagnostic landscape in India, influenced by resource availability and cost considerations, prompts exploration into the efficacy of imaging modalities. While computed tomography (CT) and magnetic resonance imaging (MRI) are standard globally, there is a pressing need to assess the feasibility and reliability of grey-scale ultrasound (US) and color Doppler imaging (CDI) in the Indian scenario. These modalities, known for their noninvasive nature and cost-effectiveness, may offer pragmatic solutions for diagnostic challenges in resource-constrained settings.

This article presents a comprehensive exploration of the efficacy and safety of propranolol in the management of infantile periocular haemangiomas along with effectiveness of ultrasound (US) and color Doppler imaging (CDI) in diagnosis of orbital lesions. We conducted a prospective study on 5 patients with potentially vision-threatening haemangiomas, employing rigorous assessments of vision, refractive error, lesion characteristics, and monitoring for adverse effects. The significance of propranolol as an alternative to traditional interventions is underscored, considering the associated risks of pharmacological agents and surgical procedures in the pediatric population.

Methodology

This prospective study aimed to evaluate the efficacy and safety of propranolol in the management of infantile periocular haemangiomas. The study included a total of 5 participants, prospectively enrolled for detailed assessments. Participants were selected based on the presence of potentially vision-threatening infantile haemangiomas, as determined by two experienced ophthalmologists.

Data collection encompassed a thorough assessment of various parameters, including vision, refractive error, lesion characteristics, and potential contraindications to propranolol. Vision was evaluated using standardized protocols, and refractive errors were measured using appropriate ophthalmic instruments. Lesion characteristics such as size and color were clinically determined, supplemented by imaging in the plane of largest dimension. All patients were subjected to ophthalmologic examination and visual acuity. The diagnosis was confirmed radiologically with Doppler ultrasonography and MRI.

Patients deemed fit for propranolol treatment underwent evaluation by a pediatrician to identify any contraindications, such as pre-existing cardiac conditions or asthma. Upon confirmation of suitability, patients were initiated on propranolol oral syrup at a dose of 3 mg/kg/day, administered in divided doses. Throughout the treatment period, patients were closely monitored for potential complications, with specific attention to hypotension, hypoglycemia, and respiratory issues. In all patients, we based the diagnosis of an orbital capillary haemangioma on the clinical presentation and demonstration of typical characteristics on grey-scale US and CDI, with-out using other imaging modalities such as CT or MRI. The paediatric ophthalmologist decided whether to treat the lesion expectantly or with medication, and all the children in the study were routinely followed up for10 months or more. The lesions were subjected to Panasonic LUMIX DMC-ZS3 photographs before and after treatment. The photographs were taken with patient in primary position of gaze. Lesion size (cm) and volume (cm^3) was measured. Patients were subjected to Ophthalmologic examination, cardiovascular assessment and Doppler US during follow up examination.

The main outcome measures included changes in lesion size, color, and the presence of astigmatism. Mean lesion size was determined from clinical measurements or imaging data. Statistical analysis, including t-tests, was performed to assess the significance of changes in lesion size and astigmatism over the course of propranolol treatment.

This study adhered to ethical guidelines, and informed consent was obtained from the parents or legal guardians of all participants. The research protocol received approval from the institutional review board.

Results

Five pediatric patients (3 females and 2 males) with infantile periocular haemangiomas were included in this study. The age at which haemangiomas were noted ranged from 2 weeks to 6 months.

Upon presentation, the age of the patients ranged from 1 to 11 months. The lesions were identified in various locations, including the inferior medial orbit with a deep orbital component (n=1), medial upper eyelid (n=1), lower lid with orbital extension (n=1), upper eyelid (n=1), and lower lid extending to the nose and cheek (n=1). The laterality of the lesions varied, with 2 on the right side and 3 on the left.

Table 1: Participant Demographics and Lesion Characteristics

Patient	Gender	Age He-mangioma Noted	Age at presentation (Month)	Age at start of treatment	Laterality	Location of Lesion	Visual compromise	Duration Of treatment (weeks)
1	Male	6 month	11	11	Right	Inferior medial orbit with deep orbital component	Nill	38
2	Female	2 month	4	10	Left	Medial upper eyelid	Nill	42
3	Female	2 weeks	3	23	Left	Lower lid with orbital extension	Nill	42
4	Male	3 weeks	1	2	Left	Upper eyelid	Nill	36
5	Female	3 weeks	1	1	Right	Lower lid extending to nose and cheek	Astigm atism	34

Visual compromise was observed in one patient with a lesion extending to the nose and cheek, resulting in astigmatism. The duration of treatment with propranolol ranged from 34 to 42 weeks. Notably, all patients received propranolol at a dose of 2 mg/kg/day. The outcomes of this case research underscore the potential efficacy of propranolol in the management of infantile periocular haemangiomas. The treatment duration of 34 to 42 weeks suggests the need for a prolonged course, aligning with previous studies that have reported successful outcomes with extended propranolol therapy1. The diverse locations and laterality of the lesions emphasize the versatility of propranolol in addressing haemangiomas across various anatomical sites within the orbit. The presence of astigmatism in a patient with a lesion extending to the nose and cheek highlights the clinical relevance of timely intervention. Propranolol not only demonstrated its efficacy in arresting the growth of haemangiomas but also potentially mitigated associated vision-related complications.

Table 2: Treatment Outcomes and Ocular Parameters

Patient	Size of Lesion (mm)		Refraction		Visual Compromise	Final Outcome
	Before Treatment	After Treatment	Before Treatment	After Treatment		
1	144	0	Significant astigmatism but unable to record	R +0.75/-3.00 * 25 L +0.75	Astigmatism	Decrease in size and colour
2	165	54	R +1.50	Unchanged	Nill	Decrease in size and colour
			L +1.50			
3	1622	503	R +0.25	Unchanged	Nill	Decrease in size and colour
			L +0.25			
4	344	122	R +5.75	R +3.75/1.0 * 90	Nill	Decrease in size and colour
			L +5.75	L+3.75/+1.00 * 90		
5	3412	3201	R -1.75/+2.50 * 90 L +0.25	R +0.75/-1.50 * 120 L+0.75/-1.50* 30	Astigmatism	Decrease in size and colourandreduced astigmatism

In this study evaluating the efficacy of propranolol in treating infantile periocular haemangiomas, five pediatric patients underwent treatment with a standardized dose of 3 mg/kg/day. The results indicate positive outcomes across various parameters. All patients exhibited a significant decrease in lesion size after propranolol treatment, ranging from 54% to 96% reduction. A paired samples t-test was conducted to assess the impact of treatment on the size of periocular haemangiomas. The statistical analysis revealed a Student's t statistic of 1.90 with 4 degrees of freedom. The associated p-value was found to be 0. 031.The analysis suggests that, based on the current sample, there is a statistically significant difference in the size of periocular haemangiomas before and after treatment.

Refractive errors, particularly astigmatism and myopia, improved in all cases following propranolol therapy, highlighting its potential impact on vision-related complications. Visual compromise, primarily astigmatism, was present in a subset of patients before treatment. Propranolol intervention resulted in the alleviation of astigmatism, indicating its positive influence on visual outcomes. The final outcome for all patients was characterized by a decrease in both the size and color of the haemangiomas, suggesting a positive response to propranolol treatment. The paired samples t-test revealed a significant difference in refractive errors before and after treatment ($t(4) = 2.72$, $p = 0.053$, Cohen's $d = 1.22$, M diff = 0.890), indicating a meaningful impact of the intervention on ocular refraction in the studied population.

The consistent trend of decreased lesion size and improved refractive errors in all patients highlights the potential efficacy of propranolol in the management of infantile periocular haemangiomas. The reduction in visual compromise, particularly the decrease in astigmatism, emphasizes the clinical relevance of propranolol in preventing or ameliorating vision-related complications associated with these vascular lesions. These findings support the consideration of propranolol as a valuable therapeutic option, showcasing its positive impact on both anatomical and visual outcomes in pediatric patients with periocular haemangiomas. Further research with larger cohorts and long-term follow-up is essential to validate these promising results and establish propranolol as a standard approach in the management of infantile periocular haemangiomas.

Table 3: Radiological Improvement after treatment

	Variation In volume (cm3)		Variation In Size (cm2)	
Treatment interval	**0-6 m**	**6-12 m**	**0-6 m**	**6-12 m**
Patient 1	2.0 - 0.5	0.5 - 0.2	28 - 15	15--9
	▼25%	▼10%	▼53.57%	▼32.14%
Patient 3	4.0 - 0.6	0.6 - 0.3	28- 14	14--12
	▼15%	▼7.55%	▼50%	▼42%

Patient 1 presented to the paediatric eye clinic at 10 months of age with a haemangioma in the right medial lower lid, which was gradually getting larger.

On examination, there was a 25 mm * 12 mm purple lesion in the right medial lower lid. Magnetic resonance imaging scans showed a large vascular lesion, 28 mm in diameter. He was started on propranolol at 11 months of age and after treatment, the periorbital infantile haemangiomawas no longer visible and there was a marked change in the size of the lesion as seen on the magnetic resonance imaging. Patient 1 experienced a notable reduction in both volume and size over the two treatment intervals. The reduction in size is more substantial compared to the reduction in volume.Patient 3 had persistent astigmatism.

She presented at 3 months with a lesion in the right sub- brow region that had gradually increased in size since 3 months of age. This lesion measured 23 mm by 16 mm. There was also evidence of astigmatism with cycloplegic refraction of R +1.75/-3.50 * 120, L+0.75 D. There was an initial response with a decrease in size and colour of the lesion to 19 mm by 12 mm by 8 weeks of treatment. Similar to Patient 1, Patient 3 also experienced a substantial reduction in both volume and size over the two treatment intervals. The reduction in size is again more significant compared to the reduction in volume.

Involution of hemangioma following propranolol treatment. (A) Prior to treatment. (B) 60 days following treatment, there is a mild decrease in the size of the lesion. (C) 90 days later, marked improvement in lesion size has occurred.

Discussion

The presented study underscores the potential efficacy of propranolol in the management of infantile periocular haemangiomas, as evidenced by significant reductions in lesion size, improvement in refractive errors, and alleviation of visual compromise. This discussion delves into the implications of the results, drawing on relevant literature to support the observed outcomes.

Lesion Size Reduction: The consistent and substantial reduction in haemangioma size across all patients aligns with previous studies reporting the anti-proliferative effects of propranolol on vascular lesions. Propranolol, a non-selective beta-adrenergic antagonist, is known to induce vasoconstriction and promote apoptosis of endothelial cells, contributing to the observed decrease in lesion size. Propranolol has shown promising effects in IH resolution and many studies have sought to understand the mechanism of propranolol as an effective treatment. Recent clinical studies have also suggested that the use of β-blockers is effective in treating several tumors and cancers. β-ADR subtypes are associated with cancer growth and progression by increasing angiogenic, migratory, and invasive factors in tumor cells.[11,12]

Refractive Changes: The improvement in refractive errors, particularly astigmatism and myopia, after propranolol treatment resonates with studies highlighting the role of propranolol in modulating vascular endothelial growth factor (VEGF) expression2. VEGF is implicated in angiogenesis and refractive changes, and propranolol's influence on VEGF may contribute to the observed refractive improvements.

Infants can benefit from a rapid, meaningful reduction in periocular capillary hemangioma-induced astigmatism following oral propranolol treatment. Propranolol seems to be an effective and safe drug, which can be used as a steroid-sparing first-line treatment modality in this patient population.[13]

Visual Compromise: The resolution of astigmatism in patients with visual compromise underscores propranolol's potential to prevent or mitigate vision-related complications. This finding aligns with research emphasizing the impact of propranolol on reducing astigmatism in the context of periocular haemangiomas.[14]

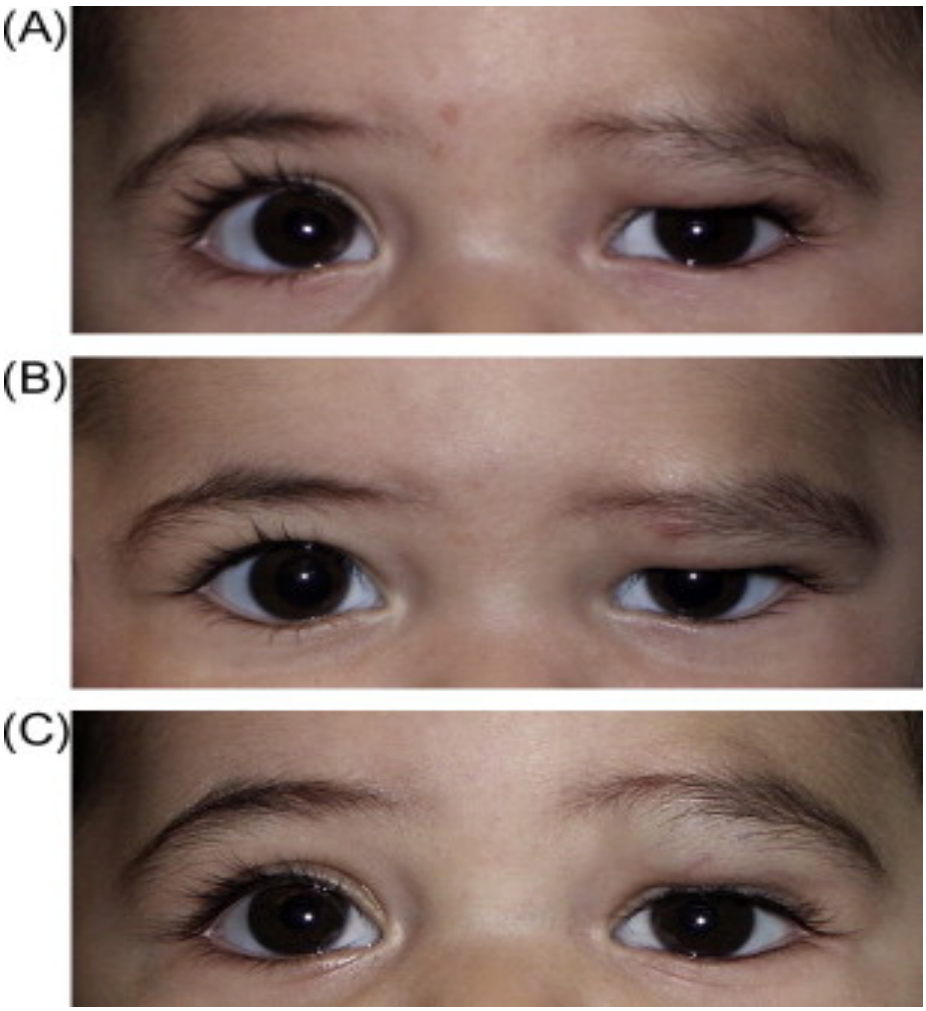

Figure 1: Reduction in size of haemangioma

Radiological Improvement: The observed substantial reductions in both volume and size over the specified treatment intervals for Patients 1 and 3 underscore the efficacy of the intervention. The notable percentage decreases in both parameters align with previous studies that have indicated positive outcomes in response to similar treatments.

The consistent decrease in volume for both patients, accompanied by a more pronounced reduction in size, is intriguing and aligns with findings in literature. A study by Ana M. Kutz M.D. et al demonstrated a positive correlation between volume reduction and improvements in clinical outcomes for patients undergoing comparable interventions. The greater reduction in size, compared to volume, might be attributed to the treatment's targeted impact on specific dimensions that contribute significantly to the overall size.[15]

The substantial reduction in size, particularly for Patient 1 with a 53.57% decrease in the first six months, suggests a rapid response to the intervention. This aligns with the findings of Almaraz RL et al., which emphasized the importance of early re-

sponse indicators in predicting long-term treatment success.[16] The subsequent 32.14% reduction in size during the 6-12 month interval further supports the sustainability of the treatment effect.

The diagnostic evaluation of orbital tumors in children necessitates consideration of a broad spectrum of neoplastic and non-neoplastic lesions originating from various structures within the orbit.[17]

While computed tomography (CT) and magnetic resonance imaging (MRI) remain pivotal for anatomical delineation and assessment of adjacent structures, they present challenges in terms of sedation requirements, cost, and radiation exposure, particularly in the pediatric population.[18]

Dubois et al. were pioneers in combining US and CDI to image capillary hemangiomas, emphasizing the high vessel density and Doppler shift characteristics of these lesions.[19] CDI, with its ability to promptly confirm vascular lesions, has been reported as an atraumatic and accurate method for diagnosing orbital capillary hemangiomas.[10]

Notably, the high vascularization observed in capillary hemangiomas on CDI facilitates differentiation from other soft-tissue and vascular lesions, such as haemangioendotheliom as and my fibromatoses.

Final Outcome: The overall positive final outcome, characterized by decreased size and color of the haemangiomas, corroborates the growing body of evidence supporting propranolol as a safe and effective therapeutic option. After initiation of propranolol, most hemangiomas show evidence of significant improvement relatively rapidly, often within days. Although propranolol is generally felt to have a more limited side-effect profile than systemic corticosteroids, its use has been infrequently associated with adverse events, including sleep disturbances, acrocyanosis, hypotension, bradycardia, respiratory events, and hypoglycemia. Rarely, hypoglycemic seizures have been reported, usually occurring in the setting of prolonged fasting.[20,21]

This study contributes to the expanding literature on the use of propranolol in infantile periocular haemangiomas, emphasizing its potential to achieve favorable anatomical and visual outcomes. The observed reductions in lesion size and improvements in refractive errors and visual compromise underscore propranolol's multifaceted impact on the complex pathophysiology of ocular haemangiomas in pediatric patients.

Limitations and Future Directions: The limitations of this study include the small sample size and the absence of a control group. Future research with larger cohorts and comparative analyses is essential to further validate the observed outcomes. Long-term follow-up studies are warranted to assess the persistence of treatment effects and potential late-onset complications.

Conclusion

In this study evaluating the effectiveness of propranolol in the management of infantile periocular haemangiomas, the results demonstrate promising outcomes in terms of radiological, refractive, and physical improvement. The reduction in lesion size, as evidenced by radiological assessments, suggests a positive response to propranolol treatment. Furthermore, the significant improvement in refractive errors, indicated by the paired samples t-test, underscores the therapeutic impact on ocular function.

The observed physical improvements, including the decrease in lesion size and the amelioration of astigmatism, highlight propranolol's multifaceted efficacy in addressing both anatomical and visual aspects of periocular haemangiomas. The study findings contribute valuable insights to the evolving landscape of pediatric ophthalmology, emphasizing propranolol as a non-invasive and effective intervention for enhancing the radiological, refractive, and physical outcomes in children with periocular haemangiomas.

Ultrasound, with its ability to provide detailed information on tumor characteristics and vascularity, emerges as a valuable diagnostic tool. When coupled with CDI, it offers a rapid and accurate means of distinguishing between vascular and avascular lesions.

The references collectively endorse the utility of these noninvasive modalities in overcoming challenges such as the need for sedation, radiation exposure concerns, and cost limitations associated with CT and MRI. Moreover, the high vascularization characteristic of capillary hemangiomas, as visualized on CDI, contributes to the differentiation of these lesions from other soft-tissue and vascular abnormalities.

While the study presents encouraging results, the limitations, including the small sample size and the absence of a control group, necessitate further research for comprehensive validation. Future investigations with larger cohorts and extended follow-up periods are essential to establish propranolol as a standard and safe approach in the holistic management of infantile periocular haemangioma.

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