Original Article

Role of Propranolol in the Management of Periocular Infantile Hemangioma

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Purpose: To find the efficacy of oral β-blocker Propranolol in the management of periocular infantile hemangioma in the pediatric population.

Study Design: Prospective interventional case series.

Place and Duration of Study: Department of Pediatric Ophthalmology, The Children's Hospital and Institute of Child Health, Lahore (Dec. 14 – Dec. 15).

Material and Methods: In this study we included 15 patients found to be suffering from vision – threatening hemangioma. Patients were evaluated as per protocol approved in our hospital adapted from international studies. All patients underwent a complete medical examination by a pediatrician, cardiologist, and a dermatologist. When needed an MRI was arranged. Oral Propranolol was initiated between one month to twelve months of age.

Results: A total of fifteen patients were treated with oral propranolol. There was a dramatic improvement with complete resolution of the lesion in 66.6% of patients. In two patients (13.3%) there was more than 50% decrease in the size of the lesion, whereas there was cessation of growth in two patients (13.3%). None of the patients developed any significant complication. The duration of drug use ranged from two to ten months, mean being 5.2 months with a standard deviation of 1.8. Propranolol was weaned off by tapering the dose over a period of two weeks on discontinuation of the drug.

Conclusions: Oral propranolol significantly reduces the size of vision threatening periocular hemangiomas with minimal or no side effects.

Key words: Peri-ocular Hemangioma, Propranolol,, Beta Blockers

Hemangioma are the most common benign soft tissue tumor of infancy. They belong to the group of congenital vascular anomalies being historically referred to as vascular birth marks[2]. This entity is seen more frequently in females, premature infants, twins and in babies born to mothers of higher maternal age[3].

The pathogenesis of hemangioma remains unclear most likely arising from hematopoietic progenitor cells. "Altered levels of matrix metalloproteinase (MMP-9) and proangiogenic factors (VEGF, b-FGF, and TGF-beta 1) appear to be responsible for the development and persistence of infantile hemangioma"[4,5]. The life cycle of hemangioma can be differentiated into three distinct developmental phases (Table 1)[2,6,7].

In majority of cases of infantile hemangiomas, only counselling and reassurance of the parents are required. However, nearly 40% of children suffering of infantile hemangioma require intervention because of serious complications.[8] Intralesional and systemic corticosteroids have been the first line medical therapy until recently in complicated and aggressive hemangiomas. In cases of steroid-unresponsive hemangiomas interferon-α and vincristine have been tried. These modalities of treatment are not free of serious and long lasting side effects. In 2008, a group of physicians from Bordeaux Children's Hospital in

Table 1: Developmental phases of Hemangiomas.

Proliferation	First three months of life. May result in ischemia, necrosis, ulceration and bleeding
Quiescence	9 – 12 months of age there is no or slow growth
Involution	This phase is heralded with a change in the color of overlying skin with shrinking of deeper components. Occurs in 70% of cases by seven years of age

France noted a regression in the size of extensive infantile hemangiomas, in patients who received treatment with propranolol for obstructive hypertrophic cardiomyopathy and high cardiac output[9]. Since then Propranolol has been used widely by dermatologist, ophthalmologist and pediatricians for the management of aggressive infantile hemangiomas.

In this article we present our experience in treating periocular and orbital hemangiomas with oral Propranolol.

MATERIAL AND METHODS

A prospective interventional study was conducted in the department of pediatric ophthalmology of Children's hospital and Institute of Child Health, Lahore between December 2014 and December 2015. All patients who presented in the pediatric ophthalmology outpatient clinic, with vision threatening infantile hemangioma, were included in the study. They were treated in accordance with the protocol adopted by the department in line with Lawley and colleagues[10] (Figure 1). A screening ECG was done in all patients. All except two patients had normal screening ECG. Both of them underwent echocardiogram with normal results as per advice of the pediatric cardiologist. Four patients had significantly large segmental facial hemangioma. They were evaluated in detail by the cardiologist, neurologist and dermatologist to rule out any systemic association. MRI of the face and head was advised in these patients. No other systemic association was identified in these patients. One patient had involvement of parotid gland as well. She began taking Propranolol after unsuccessful treatment with systemic steroids. The remaining patients received Propranolol as their initial and only intervention. Consultation was done with the pediatric cardiologist so as to determine the dose of propranolol.

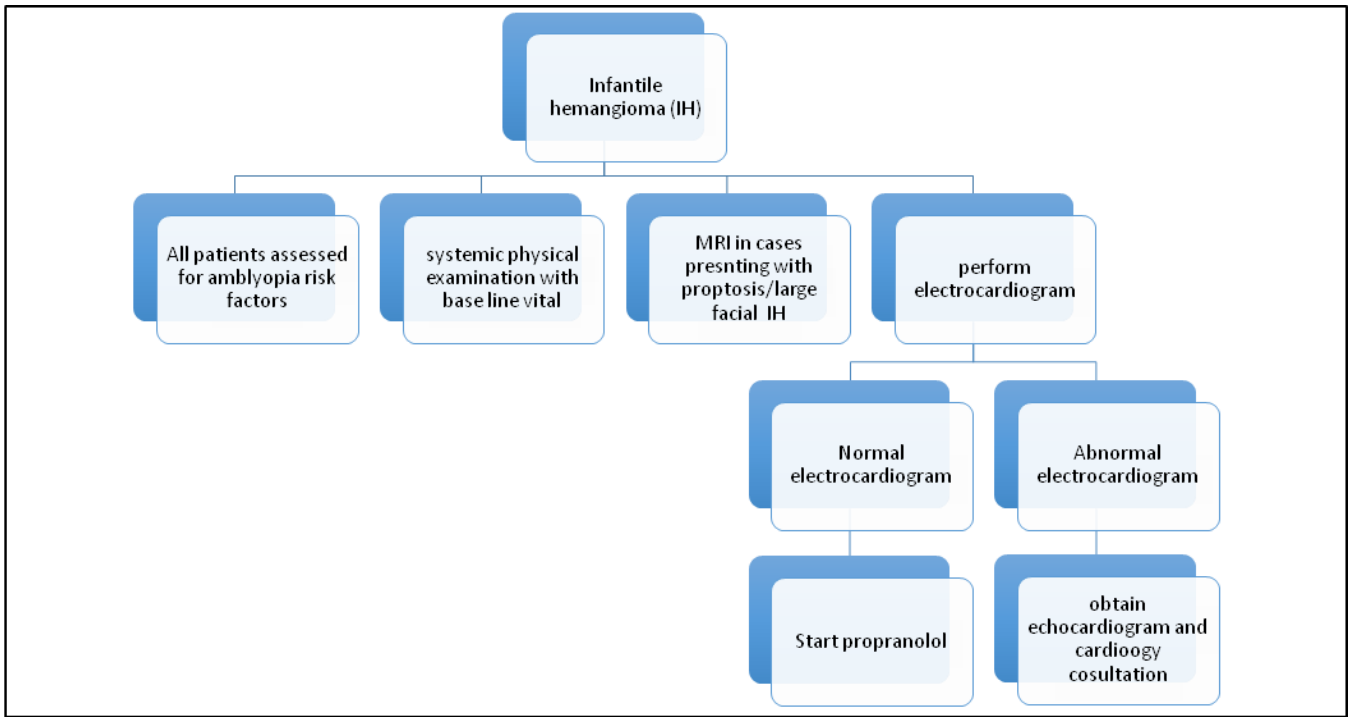


Figure 1: Pretreatment evaluation of patients.

Table 2: "Protocol for administration and discontinuation of propranolol"[1].

Preparation	10mg in the form of tablets (Instruction to the mother/guardian-crush the tablets and give the powder in divided dose, can be given to the infant mixed with honey)
Dosing	0.5mg/kg/day in 3 divided dosed as starting dose.
	1.0mg/kg/day in 3 divided dosed for the three days
	1.5mg/kg/day in 3 divided dosed for three days
	2.0mg/kg/day in 3 divided dosed for three days
Monitoring	Blood pressure/heart rate are monitored after any increase in dosage, including initial administration. Follow up every 4 – 6 weeks with serial photographs/MRI (if indicated)
Instructions to the mother/guardian	There should be minimum six – hour interval between doses- As the child may develop hypoglycemia the mother was instructed to feed the child after every dose. Parents should be educated as regards identifying signs of hypotension, bradycardia and hypoglycemia
Discontinuation	Reduce dose over 2-3 week period.

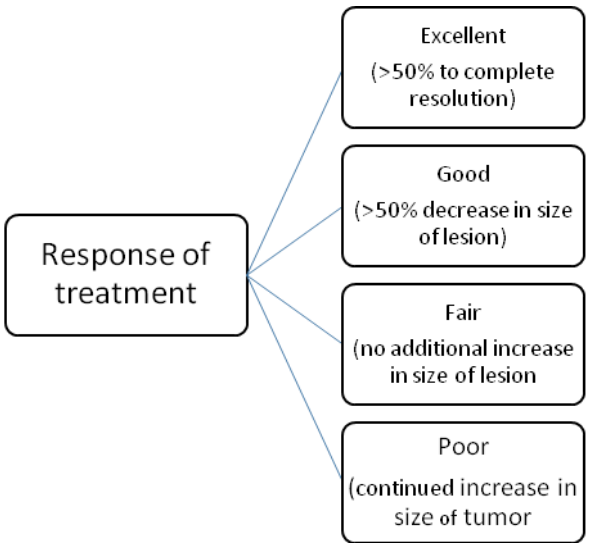


Figure 2: Grading scale of response of treatment.[1]

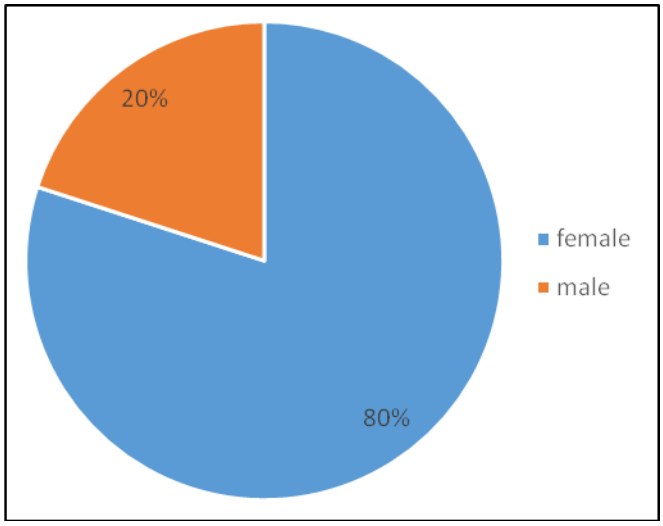
The patient was kept under observation for 4 – 6 hours after administration of first dose, so as to monitor for any change in blood pressure and heart rate. In the absence of any untoward effect he/she was allowed to go home. The infant's care givers were trained to identify signs and symptoms of adverse reaction to propranolol and were advised to have their child examined by their local primary care physician in the event of any untoward reaction of the drug. Advice was also given to the parents against abrupt discontinuation of the drug as it may result in rebound growth of the lesion. The treatment was initiated with 25% of the full dose of propranolol (0.5 mg/kg/day) slowly increasing to full maintenance dose of 2 mg/kg/day given in three divided doses (Table 2)[1]. Patients were initially monitored every two to three weeks and later every four to six weeks thereafter. Photographic documentation was done at all examinations. If need be a repeat MRI was obtained after four weeks of initiation of treatment and before cessation of treatment. The treatment continued until there was complete regression or resolution to the point of eliminating visual compromise. At this pointthe dose of Propranolol was tapered over the course of two to three weeks.

Adapting from the study published in 2010 in Journal of American academy of pediatrics ophthalmology and strabismus the results were defined as "excellent, good, fair and poor" (Figure 3)[1].

RESULTS

A total of fifteen children age one month to a year were included in the study. Mean age being 2.8 months with a standard deviation of 1.4. Out of fifteen

patients twelve were females i.e. 80% (Graph 1). Ten patients (66.6%) had involvement of the upper lid with obscuration of the visual axis. Large hemangioma involving the distribution of trigeminal nerve were seen in 3 patients (20%). There was involvement of parotid gland along with orbit in one patient (6.6%). One patient with lower lid involvement was included in the study as it was cosmetically unacceptable by the parents. The duration of treatment ranged from two to ten months. The mean duration being 5.2 months with a standard deviation of 1.8. In ten (66.6%) of the fifteen patients there was a dramatic decrease in the size of the hemangiomas (Graph 2). None of the patient experienced any significant complication. Mother of only one patient noted that the child appeared to sleep for longer hours during the first three weeks of starting the therapy.



Graph 1: Gender distribution.

Table 3: Age range of patients.

Age of Patient	N Patients
0 – 1 Month	2
1 – 2 Months	4
2 – 3 Months	4
3 – 4 Months	2
4 – 5 Months	1
5 – 6 Months	2
Mean age 3.3 months	Total = 15

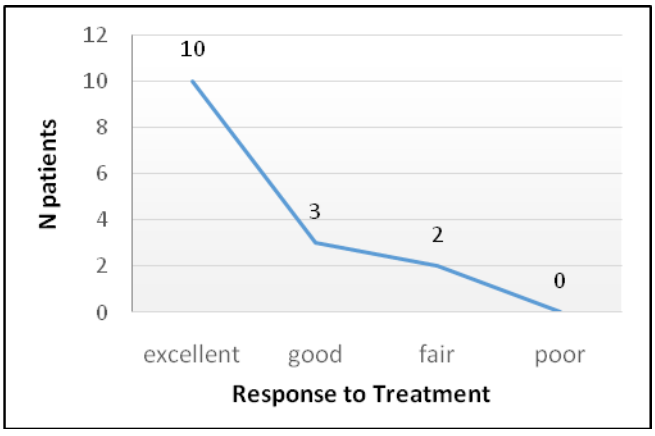
DISCUSSION

Infantile hemangiomas are often imperceptible at birth having a period of rapid proliferation followed by gradual involution[12]. Given the natural history of involution, observation and waiting is the best management of this disease entity. However, in cases where the hemangioma involves a vital structure causing a functional problem or permanent disfigurement treatment should be sought[13].

The treatment of hemangioma with intralesional and systemic steroids have frequent and even serious side effects[1,14]. Even after successful regression rebound of growth can occur following cessation of treatment with steroids[15].

Table 4: Duration of treatment.

Duration of Treatment	N Patients
2 months	2
4 months	3
5 months	2
6 months	3
7 months	1
8 months	2
10 months	2
Total number of patients	15



Graph 2: Response to propranolol.

Propranolol is commonly used by pediatric cardiologists in infants for the management of various

cardiac disorders like dysrhythmias, idiopathic hypertrophic sub-aortic stenosis, paroxysmal hypoxemic spells and congestive heart failure. Frequently seen side effects of propranolol being bradycardia, hypotension, and hypoglycemia.

A comprehensive review of literature was undertaken before starting this study so as to understand the current clinical practice for the management of infantile hemangioma. A PubMed as well as google scholar search, using the terms propranolol and infantile hemangioma yielded approximately 200 articles. Majority of these publications were retrospective reports and literature meta – analysis. Although response to therapy with propranolol was discussed in majority of articles, no definite definition and measures of response was identified. The terms used for response to therapy varied widely from "stabilization" to "complete resolution" of the lesion[16]. Positive response in all treated patients was reported in 90% of publications. Only a few articles reported treatment failures (1.6%). Thus on the basis of literature search, use of propranolol appears to be a safe modality for the treatment of periocular and orbital infantile hemangioma children[17]. The most significant and frequent reported serious complication are "asymptomatic hypotension, pulmonary symptoms related to direct blockade of adrenergic bronchodilation, hypoglycemia, hypoglycemic seizure, asymptomatic bradycardia and hyperkalemia"[18,19]. In our study 73.33% of cases had almost complete resolution of the lesion following treatment with oral propranolol whereas 13.3% showed a decrease in size of more than 50%. We did not encounter any significant side effect in our patients.

Taking into consideration the natural tendency of involution of disease the role of the pediatric

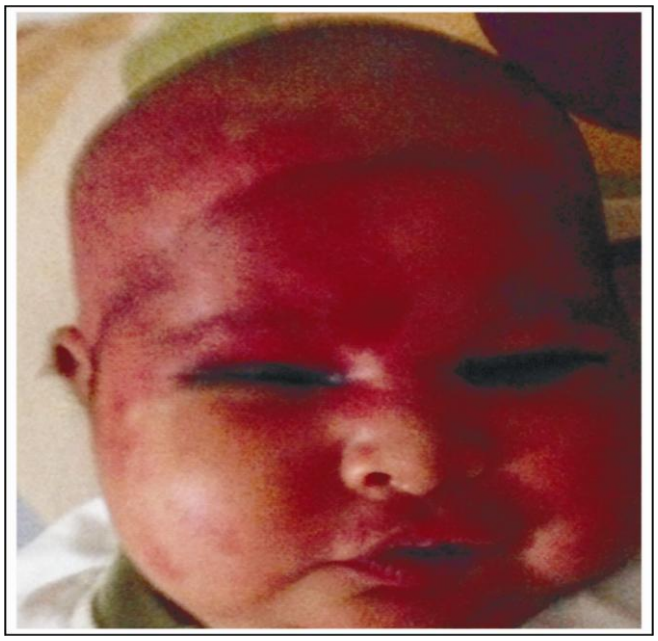


Fig 3: At birth – large facial hemangioma also involving right eye.

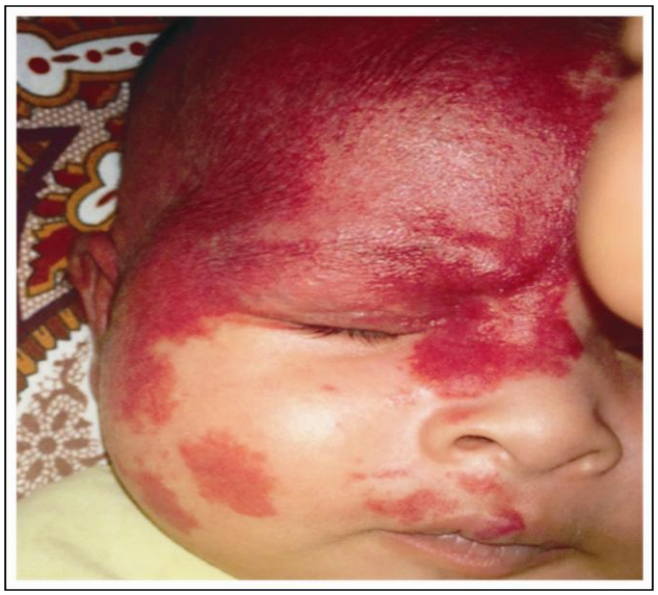


Fig 4: One month after initiation of treatment.

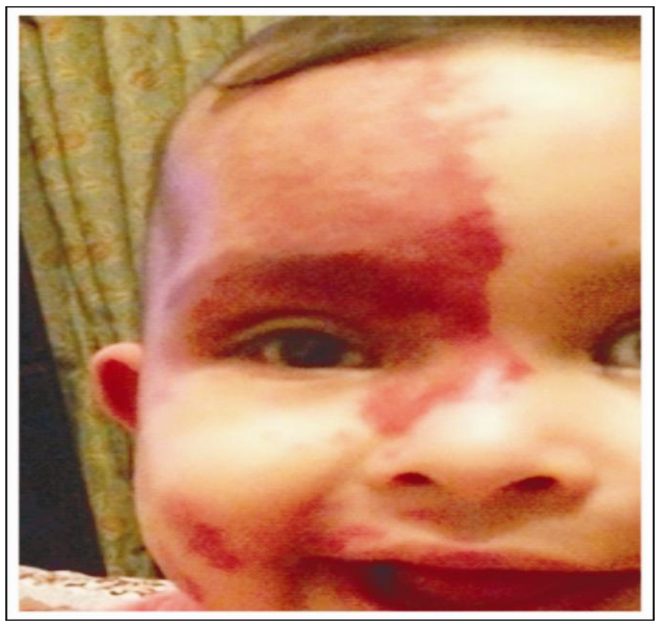


Fig 5: 4 months after initiation of treatment.

ophthalmologist is to identify which infant is at a high risk for development of complications and thus in need for systemic treatment[13]. Treatment with oral propranolol should be considered in presence of serious complications, such as impairment of visual function, proptosis and permanent disfigurement. Before the initiation of therapy, risks of adverse effects should be carefully considered and weighed against the potential benefits of treatment (Table 4)[20]. It is most appropriate to have an interdisciplinary approach involving medical, cardiac and ophthalmic team with expertise in both the management of infantile hemangioma and the use of oral propranolol in infants in order to provide the most optimal care.

Table 4: Risks of Propranolol use.

Contraindications to Propranolol	Adverse Effects of Propranolol
Cardiac shock	Hypotension
Sinus bradycardia	Hypoglycemia
Hypotension	Bradycardia
Bronchial asthma	Sleep disturbance
Heart failure	Gastro esophageal reflux
Hypersensitivity to propranolol hydrochloride	Hyperkalemia

Despite being aware of the potential side effects of propranolol we at Children's Hospital were encouraged by the reports in literature of the drug being well tolerated by infants when initiated in standard doses.

Our experience with the use of oral propranolol for the management of difficult infantile hemangioma in children has been very rewarding. We hope that our results will encourage others to further explore the safety and effectiveness of this modality of treatment.

When faced with the challenge of treating a child with infantile hemangioma following key points should be kept in mind:

- Pre-Treatment ECG should be an essential part of patient evaluation.
- The daily dose of propranolol should be divided into three doses with a minimum of six – hours interval in between.
- The propranolol dose should be slowly increased to the desired dose, starting at 0.5 mg/kg/day.
- Any change in the heart rate and blood pressure is evident during the first three to four hours after initiation of treatment so the child should be kept under observation for this period.
- A dramatic change in color is apparent within hours of the first dose of propranolol.
- Propranolol should be discontinued during intercurrent illness, especially in cases of restricted oral intake to prevent hypoglycemia.

CONCLUSION

In the absence of any serious side effects and the excellent response rate, propranolol should be considered a highly promising pharmacologic agent as first-line therapy in complicated and aggressive cases of periocular and orbital infantile hemangioma irrespective of age, site, size and stage of lesion

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Study design, manuscript review and result compilation, collection of data, manuscript writing

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