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Original Article

Propranolol for the treatment of infantile hemangioma: Our experience at The Children's Hospital, Lahore

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Abstract

Objective To assess the effect of propranolol in growing infantile hemangioma (IH).

Methods 122 children 68 girls and 54 boys, mean age 4.5 months, having IH were treated with oral propranolol. After taking baseline pulse, blood pressure, blood glucose level and echocardiography, propranolol was started at 0.5mg/kg body weight. Patients were monitored hourly for pulse, blood pressure and blood glucose level were noted and if no side effects noted for four hours, treatment was continued at home. Patients were reevaluated on day 10 and the dose was increased to 1.5-2 mg/kg daily in divided doses. Patients were followed up monthly for response and side effects. To avoid hypoglycemia in infants under the age of 3 months, mothers were advised to feed them every 2 hours.

***Result*s** The earliest effect was change in color seen in all cases. Objective clinical evidence of softening and regression were seen after 2-3 weeks. Drug was given for mean period of 6.5 months. Overall clinical response was seen in 115 (94.3%) patients. It was graded as excellent (>75% improvement) in 92 (75.4%) and good (50-75% improvement) in 23 (18.9%) patients. Adverse effects during treatment were hypoglycemia 4 (3.3%), hypotension 3 (2.5%), cold extremities 2 (1.6%) and constipation 1 (0.8%). Relapse rate was none.

Conclusion Propranolol given orally at 1.5-2.0 mg/kg/day has consistent, rapid therapeutic effect in shortening of natural course of IHs with good clinical safety.

Key words
Infantile hemangioma, propranolol.

Introduction

Infantile hemangiomas (IHs) are the most common soft tissue tumour affecting 2.6% of white infants at birth and 12% in the first year of life.[1] IHs occur more commonly in female gender, Caucasian race, low birth-weight or premature birth, and infants whose mothers underwent *in vitro* fertilization, chorionic-villus sampling during the prenatal period.[1] During initial 6 months of life the hemangiomas show fast growth, then plateau from 6-9 months and start involuting slowly after first year. It is estimated that 90% of IHs regress by the age of 9.[2]

Although IH is considered to be a self-limiting condition, an early therapeutic intervention is indicated when there is risk of permanent disfigurement, ulceration, bleeding, visual compromise, airway obstruction, congestive heart failure etc.[1,2]

Until a few years ago, corticosteroids had been the mainstay of treatment of IHs; however

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propranolol is the newer addition to the therapeutic armamentarium of IHs. Since initial report of successful use of propranolol in the treatment of IH by Léauté-Labrèze *et al*.[3] in 2008, many researchers have studied this topic and propranolol is now considered to be the drug of first choice in the management of IH. Now the indications also include cosmetically disturbing lesions e.g. large facial IHs besides the complicated IHs. The present study was planned to investigate the role of oral propranolol in the treatment of IH in our patients at The Children's Hospital, Lahore.

Methods

This study was conducted in the department of Pediatric Dermatology in collaboration with departments of Pediatric Cardiology, Pediatric ophthalmology and Pediatric ENT, Institute of Child Health/The Children's Hospital, Lahore from January 2012 to June 2014. All patients presenting with the diagnosis of IH were screened for inclusion in the study. Patients were examined by the cardiologist for any exclusion criteria i.e. contraindication to the use of propranolol. These included children with signs of a syndromal IH associated with cardiac pathology, such as PHACES (posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome), cardiac murmur, ECG abnormalities, or signs of cardiac failure, extracutaneous lesions and a very large bulky IH. Similarly, patients with asthma were also not enrolled.

After a detailed medical history and physical examination, an echocardiogram was performed in all patients. Once the treatment indication for propranolol was established, the drug was given under the supervision of pediatric cardiologist in all the patients. Propranolol was started in a dose of 0·5mg/kg daily. Patients were kept under observation for three hours and hourly pulse, blood pressure, respiratory rate and blood sugar were monitored. Then the patients were allowed to go home and mothers were advised to feed babies, especially those < 3-month old, every two hour to avoid hypoglycemia, they were also told the signs of hypoglycemia. In case of any untoward effect, they were asked to report to doctor.

Patients were called after 10 days and dose of propranolol increased to target dosage of 1.5-2.0 mg/kg daily given in three doses. After increment of the dose, patients were again kept under observation for three hours and hourly monitored for pulse rate, blood pressure, blood glucose levels. In the case of premature infants and neonates with a higher risk for hypoglycemia, renal dysfunction, cardiac morbidity and hypotension, a lower dosage of 1-1·5 mg/kg daily was used. In addition, the parents of all patients were informed about the increased risk and clinical signs of hypoglycemia i.e. pale colour, cold and clammy skin, irritability, seizures etc. They were asked to contact doctor/hospital emergency in case such signs appeared. In case of periorbital and auricular lesions, patients were also monitored by an ophthalmologist and otolaryngologist during treatment. Dressing with antibiotic ointment was used in case of ulcerated lesions.

Patients were followed up every 4 weeks, the propranolol dose was adjusted to the target dosage of 1.5-2 mg/kg daily, until the age of 9 months, after which the dose was no longer increased. During each visit, patients were assessed for clinical improvement and possible side effects. Clinical response to therapy was based on the cessation of the growth, decreases in the size, change in consistency and lightening of the color of lesions. The clinical response was

categorized into four grades as follows: 0-25% improvement (no response), 25-50% improvement (poor response), 50-75% improvement (good response) and 75-100% improvement (excellent response).

Treatment was continued till no further improvement was noted and gradually tapered in 2-3 weeks i.e. 2 weeks of two divided daily doses, 1 week of one daily dose. Treatment was stopped at the age of 12-18 months.

Chi-square and the student **t**-test were used for categorical and quantitative variables, respectively. Differences were considered significant if *p* values were less than 0.05.

Results

122 children, 68 girls and 54 boys, female to male ratio of 1.3:1 were enrolled in the study. The mean age of children was 4.5 months. The distribution of lesions is shown in **Table 1**. 82.8% of IHs were located in the head and neck region. 19 (15.6%) patients were premature babies. The indications for treatment are shown in **Table 2**. The majority (51.6%) sought treatment for cosmetic reasons. Lesions were ulcerated in 22 (18%) cases.

Treatment was efficacious in 115 of the 122 (94·3%) patients (**Table 4**). It was graded as excellent in 92 (75.4%) and good in 23 (18.9%) cases. Within 72 hours, a visible change in colour was noticed in all patients. Change in consistency i.e. softening followed the colour change whereas growth cessation and volume reduction occurred more slowly, becoming visible after a few weeks. In 5 (4.3%) patients the effect became apparent within 2-3 weeks. The ulcerated lesions also started healing within 3-4 weeks. The duration of treatment varied from 3 to 9 months with a mean of 6.5 months.

After achieving the maximum therapeutic effect, the drug was slowly tapered in 2-3 weeks. Relapse was not seen in any patient. The response was good in smaller lesions (<2cm

Table 1. Characteristics of infantile hemangioma (IH) (*n*=122).

Characteristic	*N (%)*
Growth pattern	
Superficial macular	13 (10.7)
Superficial nodular	102 (83.6)
Deep	-
Mixed	7 (5.7)
Localization	
Head/neck	101 (82.8)
Eyelids/periorbital	37 (30.3)
Nose/perinasal	21 (17.2)
Lips/perioral	18 (14.8)
Ear/periauricular	8 (6.6)
Cheek	7 (5.7)
Forehead	3 (2.5)
Neck	3 (2.5)
Scalp	2 (1.6)
Beard area	2 (1.6)
Diaper area	9 (7.4)
Extremities	7 (5.7)
Trunk	5 (4.1)

Table 2 Indications for treatment (n=122).

Characteristic	*N (%)*
Cosmetic risk, face deformity	63 (51.6)
Impending visual impairment	24 (19.7)
Ulceration	22 (18.0)
Impending nasal obstruction	13 (10.7)

Table 3 Clinical response to propranolol therapy in infantile hemangioma (n=122).

Clinical response	*N (%)*
Excellent (75-100% response)	92 (75.4)
Good (50-75% response)	23 (18.9)
Poor (25-50% response)	5 (4.1)
No response (<25% response)	2 (1.6)

Table 4 Adverse effects observed during propranolol treatment (n=122).

Side effects	*N (%)*
Hypoglycemia	4
Hypotension	3
Cold extremities	2
Constipation	1

diameter), younger patients (< 6 months) and head and neck region (p<0.05).

Amongst the 7 (5.7%) non-responders, one patient showed no improvement as he had already received intralesional corticosteroid and atrophic scarring had occurred. Another patient showed no improvement as he was started propranolol treatment at 1.4 years of age.

Table 4 shows the adverse effects of treatment. The most common adverse effect of propranolol, observed in 4 (3.3%) patients was hypoglycemia which clinically manifested as cold and clammy skin and increased irritability. Patients were asked to report to hospital emergency for blood glucose level estimation and management. However, the treatment was continued and mothers were asked to feed their children every two hours. Mild hypotension was recorded in 3 (2.5%) patients but same dose was maintained after consultation with the cardiologist and the condition improved gradually. Two (1.6%) patients developed cold extremities and 1 (0.8%) constipation. These adverse effects occurred in the early phase of treatment and did not warrant discontinuation of treatment.

Discussion

The currently available data suggests propranolol to be more successful for the treatment of IH than other available modalities.[4] The present study was undertaken to assess the use of propranolol in our patients of IHs.

Our study showed very promising results. Propranolol was effective in 94.3% of patients. We treated IHs at all locations and indications including cosmetic concern; however, IHs that were very large, had associated cardiac comorbidity or located on extracutaneous sites were excluded. The colour started to change within 72 hours, followed by softening and reduction in size which manifested after a few weeks. The improvement continued in subsequent months. Results were better in younger patients, who were aged < 6months. This sequence of events corresponds to the mechanism of action.[5]

Our results are in accordance with many studies and meta analysis.[6-15] All these studies reported a response rate of over 90%. Propranolol showed excellent efficacy in all types and locations of IHs. In an extensive review of 1175 cases of IHs treated with oral propranolol showed a success rate of 98.4%; however, measures of response varied widely, from stabilization to complete response. Similarly different studies used different protocols about starting dose, dose escalation and monitoring of treatment from extensive monitoring to little or no monitoring. The mean and median ages at initiation of therapy were 5.1 months and 4 months, respectively.[6]

In a retrospective study by Luo *et al*.[7] 635 patients underwent oral propranolol treatment for IH. The efficacy rate was 91.2% and 162 of the patients recovered completely. No significant adverse effects were observed and the overall incidence of adverse effects was 2.1%. Sagi *et al*.[8] treated 99 patients of IHs with propranolol with a success rate of 98.8%. Mild side effects occurred in 32% of patients. Recurrence occurred in 13% of patients. Andersen *et al*.[9] used 1mg/kg daily and reported a clearance of 97%.

We noticed a better response in smaller lesions, younger patients in whom treatment was started before the age of 6 months and head and neck lesions. A similar observation was made by Sagi *et al*.[8] that lesions located on the face are better responders when treatment is started early.

Treatment should continue up to age 12-15 months, with a longer course for segmental or deep hemangiomas. This implies that early initiation of treatment, before rapid expansion of the tumour, may give better cosmetic results.[2,13] Similarly, for ulcerated IHs an early treatment shortens the ulceration time.[14]

Propranolol is a nonselective beta-adrenergic antagonist with an inhibitory effect on both β1- and β2-adrenoceptors with similar affinity. Its therapeutic effect in IH can be attributed to different mechanisms i.e. vasoconstriction due to decreased production of nitric oxide; inhibition of angiogenesis by downregulation of angiogenic factors, vascular endothelial growth factor and basic fibroblast growth factor; and induction of apoptosis of capillary endothelial cells. These mechanisms correspond, respectively, with the following clinical observations: softening and fading, cessation of growth, and long-term regression.[5]

According to the guidelines designed for propranolol treatment in the infantile hemangiomas, a target dosage of 2-3 mg/kg daily is considered a safe and effective dosage for the healthy infants.[6] Another study recommended a minimal dosage of 1·5-2.0 mg/kg daily to induce involution.[15] Andersen *et al*.[9] used 1mg/kg daily and reported a response of 97%. We used an intermediate dosage of 1.5-2.0 mg/kg in our patients and it proved quite effective. Some studies have suggested a dose up to 3mg/kg/day in case of airway hemangioma.[16] It implies that the target dose has to be tailored according to the clinical response of the patient, starting from a lower dose.

Treatment duration ranged from 3 to 9 months in our study. Some researchers used propranolol for longer periods than us e.g. 8.5±3.2 months by Sagi *et al*.[8] and 10·7 months by Hermans *et al*.[10] Treatment duration may vary according to the type of IH and the specific treatment indication. In deep and mixed IHs the proliferation phase starts and stops later, so the treatment has to be continued until the age of 12-16 months. Similarly, duration of therapy is prolonged in case of ulceration and locations e.g. deep periorbital IHs and airway IHs. The shorter duration of treatment may be explained by the relatively higher number of superficial IHs in our study.

Similarly, at the end of the treatment period, a slow reduction of the dose in 2 or 3 weeks is indicated, as abrupt discontinuation of ß-blockers carries the risk of rebound cardiac hyper-reactivity due to upregulation of beta-receptors.[11] Similarly, in a variable number of patients there can be recurrence of IH which may require a second course of propranolol. Sometimes the residual fibrofatty tissue may mimic a recurrence to an unwary eye. Incidentally, we did not find a relapse, an observation not reported previously. Whether it was due to shorter follow-up, different study population or true drug-related efficacy is difficult to commend.

Regarding the safety of propranolol therapy, 10 adverse effects were seen in 122 patients. These were manageable and did not warrant discontinuation of therapy. These findings are also consistent with previous studies which recorded similar profile but with different frequencies.[6-8]

ß-Blockers have a well-documented safety and side-effect profile in children aged < 7 years.[17] The main side-effects of propranolol are bradycardia, hypotension and hypoglycemia. Bronchospasm, rash, gastrointestinal symptoms, fatigue, behavioural changes, peripheral vasoconstriction and sleep disturbances are seen

less frequently. The most serious side-effect of propranolol use in IHs is hypoglycemia especially seen in patients aged < 3 months with decreased food intake or concomitant treatment with oral corticosteroids, during tapering phase. In such situation frequent monitoring and feeding are recommended.[11,13] In our patients, 4 cases of hypoglycemia were seen. Patients who are managed as outpatient, it is imperative to teach parents the signs of hypoglycemia for early diagnosis. Propranolol also diminishes cardiac activity, causes bradycardia and hypotension and can, thus masks the clinical signs of cardiac failure.[11,13,18] This necessitates a special care in patients with cardiac comorbidity. A pretreatment screening to rule out cardiac problems is necessary.

All of our patients were treated on outdoor basis except for three-hour supervision and monitoring at the start of treatment and then at the time of dose increment. At home protocol may be followed in patients born at term, with normal birth weight and no abnormalities on physical examination or ECG. In all other cases, treatment should be started in hospital.

Conclusion

In our study population, propranolol was effective and safe in vast majority of patients. It is definitely a valuable and promising therapeutic modality for IH; however, dose adjustments may be required to avoid adverse effects.

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