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Original Article

Propranolol for infantile hemangioma: An evaluation of its efficacy and safety in Iranian infants

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ABSTRACT

***Background*:** Propranolol has been recently indicated to inhibit the rapid growth and involution of infantile hemangioma. In the present study, we investigated the efficacy and safety of propranolol in Iranian infants.

***Methods*:** A total of 30 infants with indications for medical intervention, such as large hemangiomas, wounds with or without secondary infection, or active trauma-induced bleeding, were selected. First, a total concentration of 1 mg/kg/day was orally administered to the infants; the dosage further increased (2-3 mg/kg/day) in case the infants experienced no adverse effects. Following weekly (one month after treatment) and monthly (up to six months) follow-ups, hemangioma activity score (HAS) was calculated to evaluate swelling, color of the lesion, and ulcer size.

***Results*:** In the present study, infants with the mean age of 5.33±3.50 years received therapy. Improvement was observed in the lesions of all patients, characterized by a significant decline in size, change in color, and reduction in ulcer size (P<0.001). No serious adverse effects were recorded, except agitation which was overcome by reducing the drug concentration.

Conclusion: It seems that propranolol can be considered as an efficacious and safe alternative to other pharmaceutical and surgical interventions for infantile hemangiomas in Iranian infants.

Keywords: Hemangioma, Hemangioma activity score, Infants, Propranolol

Introduction

Infantile hemangioma (IH) refers to vascular tumors with obvious characteristics such as rapid proliferation, as well as slow occasional involution (1). Nevertheless, most hemangiomas demonstrate spontaneous healing without any medical inter-ventions. According to the literature, roughly 10% of IHs lead to morbidity due to ulceration or involvement of respiratory, cardiac, and ocular systems (1-3).

Therapeutic interventions for severe IH include steroids, chemotherapeutic agents, laser therapy, and surgery (3, 4). However, a wide spectrum of side-effects (i.e., altered growth, moon facies, osteoporosis, fungal infections, and hypertension) is associated with these therapeutic options, which can in turn lead to unresponsiveness to treatment in patients (5, 6).

Recent treatments have shifted to beta-blocker propranolol, with an efficacy rate much higher than conventional steroids (95% vs. 70%) (7). The potential adverse effects in response to beta blockers were predominantly limited to manageable hypotension, bradycardia, diarrhea, and fatigue (8). Yet, it was indicated that beta-blocker propranolol in children probably causes asymptomatic hypoglycemia and lethargy (8-10). Moreover, race and ethnicity are well correlated with Subtype of hemangioma and incidence rate (11). Therefore, more caution and research are required regarding the safety of propranolol. In the present study, we aimed to determine the efficacy and safety of propranolol in 30 light-skinned Iranian children with IH.

Methods

Patient selection and pretreatment evaluation

IHs with indications for medical intervention, such as large hemangiomas with aesthetic derangement, involvement of ocular, genital, oropharyngeal, and pharyngeal regions (leading to life-threatening or disabling complications), wounds (with or without secondary infection), and active

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trauma-induced bleeding were evaluated in this study.

1) posterior fossa malformations–hemangiomas–arterial anomalies–cardiac defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome (PHACE syndrome); 2) major cerebrovascular lesions on magnetic resonance imaging (MRI); 3) ejection fraction (EF) ≤ 60% on echocardiography; 4) bradycardia (heart rate < 60%); 5) hypotension (systolic blood pressure < 100 mmHg); and 6) history of asthma or hypoglycemia.

Written informed consents were obtained from the infants' parents, and the demographic questionnaire was completed after explaining the treatment procedure.

Drug preparation and monitoring during treatment

The propranolol tablet (10 mg; Tolid Daru Co., Iran) was diluted in water. A total concentration of 1 mg/kg/day was orally administered to the infants; the dosage increased to 2-3 mg/kg/day within a few days if the infant experienced no adverse side-effects during inpatient monitoring. A treatment period of six months was scheduled for the infants. Hypoglycemia, cardiologic, and respiratory monitoring was performed during the first two or three days of treatment one to three times a day. Further monitoring was conducted each week over the first month; afterwards, monthly follow-ups were scheduled until the end of the treatment period.

Hemangioma activity score (HAS)

HAS was used at two time points (t_0 before treatment and t_1 at the end of treatment) by two dermatologists for scoring the proliferative activity of hemangioma and evaluating the extent of deep swelling, color of IH, and ulceration, based on images captured in each visit (Table 1) (12).

Table 1. Hemangioma activity score (HAS*)*

		Score
Swelling score	Tense swelling	6
	No tense swelling at t_0 or < 50% reduction in the follow-up	4
	≥ 50% reduction in the follow-up	2
	No swelling in the follow-up	0
Color	Bright/shining redness	5
	bright/shining red edges	4
	Matte red or reddish purple	3
	Blue or shining deep blue	2
	Gray	1
	Skin-colored after activity	0
Ulceration	≤ 1 cm^2	0.5
	1-2.5 cm^2	1
	≥ 2.5 cm^2	2

Statistical analysis

In this study, qualitative variables are expressed as percentage, whereas quantitative variables are presented as mean±SD. Kolmogorov-Smirnov test was utilized to check the normal distribution of the data. The mean HAS scores obtained at two time points were collated between observers, using paired samples t-test or Wilcoxon signed-rank test. P-value less than 0.05 was considered statistically significant. For statistical analysis, SPSS version 16.0 was used.

Results

A total of 30 patients (80% female and 20% male; age range: 1.5–18 months) were enrolled in the study. The infants' body weight ranged from 4.5 to 11.5 kg (6.4±1.2 kg). The subjects' age at the onset of therapy ranged between 5 and 24 months (mean age: 13.06± 4.65 months). Based on the findings, the mean maternal age was 28.16±4.85 years.

Overall, 60% of the subjects were the first children of the family. The majority of the infants (93.3%) had no family history of the disease (Table 2). The average scores of swelling at t_1 (six months of treatment) and t_0 were 0.7667 and 3.8667, respectively (P<0.001). As for the color, the average scores at t_1 and t_0 were 0.4 and 4.45, respectively (P<0.001). The mean score of ulceration at t_1 was measured to be 0.00, whereas the score at t_0 was 0.13±0.26 (P<0.001).

Finally, HAS scores at t_0 and t_1 (six months of treatment with propranolol) were 4.62±0.61 and 0.72±1.11, respectively, indicating a statistically significant difference between pre- and post-drug therapy periods (P=0.001) (Table 3). No known adverse events, associated with propranolol, were recorded, except agitation in two patients which was overcome by reducing the drug dosage).

Table 2. Demographic characteristics of the infants under study

Parameters		Hemangioma (N=30)
Gender	Female	24
	Male	6
Duration of treatment (months)		13.06±4.65
Mother's age (years)		28.16±4.85
Weight (kg)		6.4±1.2
Infant's age (months)		5.33±3.5
Child order	First	20
	Second	6
	Third	3
	Last	1
Family history	Yes	2
	No	28

Table 3. Comparison of hemangioma activity scores (HAS) in 30 cases of infantile hemangioma at t_0 and t_1 via paired samples t-test or Wilcoxon signed-rank test

Factors	Mean± SD	P-value
Edema at t_0	3.8±1.9	<0.001
Edema at t_1	0.76±1.3	
Color at t_0	4.45±1.03	<0.001
Color at t_1	0.4±0.81	
Ulcer at t_0	0.13±0.26	<0.001
Ulcer at t_1	0.00±0.00	
HAS at t_0	4.62±0.61	<0.001
HAS at t_1	0.72±1.11	

Discussion

As for hemangioma, systemic corticosteroids and vincristine have been shown to be effective. Nevertheless, children seem to be prone to some adverse effects such as growth retardation, hypercortisolism, central retinal artery occlusion, eyelid necrosis, and gastric upset (13, 14). In this regard, Léauté-Labrèze et al., as French pioneers, designed some experiments to evaluate the impact of propranolol on the treatment and management of IHs (15).

The mechanism of action in propranolol is applied via inhibiting the release of nitric oxide, initiating the apoptosis of capillary endothelial cells, and interfering with the gene expression of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and metallo-proteinase matrix (15-17).

To the best of our knowledge, this is the first study on the efficacy and safety of propranolol therapy for IH as first-line treatment in Iran. We used 2-3 mg/kg/day of propranolol for six months, while in several studies, most practitioners preferred a dose range of 1-3 mg/kg/day (18-20). The reported duration of therapy (range: 4 weeks to 12 months) depends on the IH type and response rate (21-23).

Also, we utilized the HAS system for scoring the proliferative phase of hemangioma, as proposed by Janmohamed et al. and found it to be a practical and simple system for evaluating the treatment results (12). Our findings showed that propranolol administration is associated with a significant decline in deep swelling and change in ulcer color and size. This finding was consistent with a previous report where hemangioma volume diminished during six months of therapy (15, 24, 25).

No serious side-effects, which could inhibit the process of therapy, were observed in our study population. Regular monitoring indicated no intolerance or safety issues related to the use of propranolol. However, we encountered two cases of agitation, which were managed through reducing the therapeutic dosage. The present study support the findings reported by most published papers in which the safety of propranolol in IH treatment was evaluated (24, 26)

Conclusion

Based on the findings, oral propranolol administration was found to be effective in the treatment and management of IH in Iranian children, similar to the majority of other ethnic groups. This agent showed acceptable tolerance and minimal adverse effects.

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Conflicts of interests

The authors declare no conflicts of interest in relation to this study.

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