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Medical Management of Infantile Hemangioma: Is oral Propranolol Superior to Oral Prednisolone?

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Abstract

Objective: To compare the efficacy of oral propranolol versus oral prednisolone for treating infantile hemangioma.
Methodology: This randomized controlled trial was conducted at the Department of Plastic Surgery, Pakistan Institute of Medical Sciences (PIMS), Islamabad from January 2015 to December 2016. Written informed consent was taken from the parents. The trial included 80 patients who were randomly assigned to two treatment groups, each comprising of 40 patients. Patients in Group-A received oral propranolol treatment, whereas patients in the Group-B received oral prednisolone treatment. Greater than 75% regression in size (as determined by the length, width, and height measured in millimeters) of the hemangioma as compared to the pre-treatment status was determined for each group and comparisons were drawn. The percentages of various outcome variables were compared by employing chi-square test. A p-value of less than or equal to 0.05 was regarded as statistically significant.
Results: The age of the children ranged from 1-36 months, with a mean of 15.20±10.40 months. The majority (n=51, 63.8%) of them were aged between 1-18 months. There were 33 (41.3%) male whereas 47 (58.7%) female children. Maximal possible matching of the two groups was ensured with regards to the various demographic and clinical entry parameters. The frequency of efficacy was significantly higher (92.5% vs. 25.0%; p=0.000) with propranolol as compared to prednisolone. Similar significant difference was seen across all age and gender groups.
Conclusion: Propranolol had superior efficacy, 6-weeks post-treatment irrespective of the patients' age and gender. Hence, oral propranolol should be the preferred choice for treating infantile hemangiomas.
Key words: Infantile hemangioma, Oral propranolol, Oral prednisolone, Efficacy of treatment.

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Introduction

Infantile hemangiomas (IHs) are the most common benign vascular tumors of infancy, affecting 5-10% of infants. IHs manifest as small lesions within the first 2 months of life, followed by a rapid proliferation phase (2 months to 12- months), a spontaneous involution phase (2-years to 10 years), and then the involuted phase (up to 12 years). Cosmetically mutilating scars or residual fibro fatty tissue can persist after the lesions have involuted. [1-5]

Intervention is indicated in IHs that may endanger vital functions, result in permanent disfigurement, or cause parental concern. About 10% of IHs result in local complications corresponding to their anatomic locales. For instance, life threatening airway obstruction (IHs of the larynx and the sub glottis), strabismus, astigmatism and permanent amblyopia (caused by IHs of the upper eye lids), deformation of external ear and temporary conductive hearing loss (IHs of the pinna) and bleeding ulcers (IHs of anogenital and oral regions). Approximately 1% of IHs result in life threatening systemic complications such as congestive heart failure

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with anemia and hepatomegaly.[1,5,6]

Many pharmacologic agents have been tested for addressing the IHs. These include corticosteroids (oral, intralesional, topical), propranolol, interferon alfa-2a, vincristine, cyclophosphamide, Imiquimod and Pulsed dye laser (PDL). Until lately, oral prednisolone has been the mainstay of treatment.[1,2,7,8] Since the initial report of unexpected discovery of propranolol for the treatment of IH in 2008, there has been a flurry of successful case reports and case series describing it to be rapidly effective, well tolerated, and better than the previous therapies.[9-12] However, its adverse effects (such as growth retardation, Cushing like syndrome, diabetes mellitus, hypertension, avascular necrosis of hip and compromised immunity) are insidious and hard to monitor. Propranolol's action on IHs is attributable to vasoconstriction, inhibition of angiogenesis and induction of apoptosis.[8-12]

Internationally, there is growing awareness about the significant consequences of IHs and there is growing interest in evaluating the comparative efficacy and safety of various therapeutic regimens for their management.[10-17] However, no such study has been conducted in Pakistan to date. This study is intended to evaluate the efficacy of oral propranolol versus oral prednisolone in our population. We aimed to evolve a useful evidence base in this regard and hence help to improve the overall outcome of the management of IHs amongst our children.

Material and Methods

This randomized controlled trial was conducted at the Department of Plastic Surgery, Pakistan Institute of Medical Sciences (PIMS), Islamabad from January 2015 to December 2016. Ethical approval was taken from the Hospital Ethics Committee. Written informed consent was taken from the parents of the children. A total of 80 patients were randomly allocated by non-probability consecutive sampling to either of the two groups, using computer generated table of random numbers.

Inclusion criteria: Children of either gender and any age presenting with infantile hemangioma (IH) ≥ 1 cm in length, height, and width, and with one or more of the following indications for early intervention: 1) Visual field disruption presenting as strabismus and astigmatism; 2) respiratory obstruction presenting as stridor and respiratory failure; 3) congestive heart failure presenting as cyanosis and dyspnea; 4) hemorrhage presenting as visible bleeding, and 5) serious disfigurement of aesthetic areas such as face and nose.

Exclusion criteria: The following were excluded from the study: Neonates, family history of atopy, recurrent wheezing, infants with Type 1 diabetes mellitus, reactive airways, underlying circulatory disorders (i.e., hypotension, heart failure, cardiogenic shock, sinus bradycardia and 2nd/3rd degree heart block). Infants with documented hypersensitivity to propranolol or who had already received any kind of specific treatment at some other health care facilities were also excluded.

The patients were assessed by adequate history, a thorough examination and relevant investigations. The size of the IH was documented. All the patients having IH were referred to cardiology clinic for baseline clinical observation of pulse, blood pressure, respiratory rate, electrocardiography recording and echocardiography to rule out any potential contraindication to propranolol therapy. The treatment protocol for each group was as follows:

Oral Propranolol group: Propranolol treatment regimen started with the oral administration of initial loading dose of one third of the calculated 2mg/kg/day dose. Parents were instructed to feed the child regularly and to avoid prolonged fast. After the initial dose, infant was kept under four-hour observation in the hospital for hourly monitoring of the vitals. The dose was increased to target dose of 2mg/kg/day on follow-up on 3rd day followed by vitals monitoring after half hour of dose administration. From then on, the child was followed every fortnightly with response assessed by measurement of decrease in size of the lesion. Parents were instructed to consult the treating physician at once if the child had a serious cough with dyspnea. At the end of 4-weeks treatment, propranolol therapy was tapered over a 2-week period to minimize the risk of a hyperadrenergic withdrawal response.

Oral Prednisolone group: The oral prednisolone treatment regimen started with oral administration of 4mg/kg/day prednisolone till 4 weeks before gradually tapering off the drug over 2 weeks period.

Follow up after completion of the therapy was done at 6-weeks. All the observations along with demographic information of patients, various interventional treatments undertaken and complications observed were documented.

All the data recorded were subjected to statistical analysis using the computer software SPSS version 17. Descriptive statistics were used to calculate frequencies, percentages, means and standard deviation. The numerical data such as age was expressed as Mean ± Standard deviation while the categorical data such as the gender of patients and efficacy were expressed as frequency and percentages. The percentages of various outcome variables were compared by employing chi-square test. A p-value of less than or equal to 0.05 was regarded as statistically significant.

Results

The age of the patients ranged from 1 month to 36 months, with a mean of 15.20±10.40 months. The majority of the patients (n=51, 63.8%) were aged between 1-18 months, whereas others were aged between 19-36 months (n=29, 36.2%). There were 33 (41.3%) male and 47 (58.7%) female children. There was no significant difference between the two groups in terms of mean age (p = 0.898), age (p = 0.816), and gender (p = 0.496) groups distribution as shown in Table I.

Table I: Baseline demographic features of the children included in the two groups.(n=40)

Characteristics	Propranolol (n=40)	Prednisolone (n=40)	*p-value*
Age (months)	15.35±10.60	15.05±10.34	0.898
Age groups			
1-18 months	26 (65.0%)	25 (62.5%)	
19-36 months	14 (35.0%)	15 (37.5%)	0.816
Gender			
Male	15 (37.5%)	18 (45.0%)	
Female	25 (62.5%)	22 (55.0%)	0.496

Table II: Comparison of the frequency of efficacy of oral propranolol and oral prednisolone groups. (n=40 patients in each group)

Efficacy	Study Group		Total	*p-value*
	Propranolol (n=40)	Prednisolone (n=40)		
Yes	37 (92.5%)	10 (25.0%)	47 (58.8%)	0.000*
No	3 (7.5%)	30 (75.0%)	33 (41.3%)	
Total	40 (100%)	40 (100%)	80 (100%)	

Chi-square test, * Observed difference was statistically significant.

The frequency of efficacy was significantly higher with propranolol (92.5% vs. 25.0%; p=0.000) as compared to prednisolone as shown in Table II. Similarly, significant difference was seen across all age and gender groups as shown in Table III and Table IV respectively.

Discussion

Infantile hemangioma (IH) is a common pediatric problem that results in cosmetically disfiguring scars in a number of patients. Since long, oral prednisolone had been the mainstay of treatment of treatment.[3-6] Our study found oral propranolol to be highly effective for treating IHs at a dose of 2mg/kg/day in divided doses without any major

Table III: Comparison of Frequency of Efficacy of Propranolol and Prednisolone StudyGroups across Age Groups.

Age groups	Efficacy	Study group		Total	*p-value*
		Propranolol (n=40)	Prednisolone (n=40)		
1-18 Months (n=51)	Yes	24 (92.3%)	6 (24.0%)	30(58.8%)	0.000*
	No	2 (7.7%)	19 (76.0%)	21(41.2%)	
	Total	26(100.0%)	25(100.0%)	51(100.0%)	
19-36 Months (n=29)	Yes	13 (92.9%)	4 (26.7%)	17(58.6%)	0.000*
	No	1 (7.1%)	11 (73.3%)	12(41.4%)	
	Total	14(100.0%)	15(100.0%)	29(100.0%)	

Chi-square test, * Observed difference was statistically significant

Table IV: Comparison of Frequency of Efficacy of Propranolol and Prednisolone StudyGroups across Gender

Gender	Efficacy	Study Group		Total	*p-value*
		Propranolol (n=40)	Prednisolone (n=40)		
Male (n=33)	Yes	14 (93.3%)	5 (27.8%)	19(57.6%)	0.000*
	No	1 (6.7%)	13 (72.2%)	14(42.4%)	
	Total	15(100.0%)	18 (100.0%)	33(100.0%)	
Female (n=47)	Yes	23 (92.0%)	5 (22.7%)	28(59.6%)	0.000*
	No	2 (8.0%)	17 (77.3%)	19(40.4%)	
	Total	25 (100.0%)	22 (100.0%)	47 100.0%)	

side effects. Systemic corticosteroids have been considered as the first-line therapy for treating large or life-threatening infantile hemangiomas since the early twentieth century. However, this has changed with the recent advent of propranolol in treating severe hemangioma of infancy.[7-15,18] Izadpanah et al[11] conducted meta-analysis of 16 studies that employed oral corticosteroid for treating IH and compared it with a meta-analysis of 35 studies that used propranolol for treating IH. This comparison between corticosteroids and propranolol in response rate demonstrated statistical significance in favour of propranolol (71.0% versus 97.3% respectively; $p < 0.0001$).

In a research conducted in Edinburgh, U.K, Szychta et al[19] performed a prospective cohort study on 60 children. They found that the average final volume of IH after treatment with propranolol was significantly lower than the average initial volume ($p = 0.0343$). They observed only minor side effects (transient asymptomatic hypotension, diarrhea, sleep disturbances, and a rash on the torso) during propranolol therapy. They concluded that propranolol is an effective, well-tolerated, and safe first-line treatment for proliferative hemangioma. They recommended that therapy should be commenced early, continued with the target dosage of 2 mg/kg/day in three divided doses through the proliferative phase of infantile hemangioma, and stopped gradually.

A study conducted by Anderson et al[20] reported 97% effectiveness of propranolol with majority of patients treated at a low dose of 1mg/kg/day. No relationship was found between location of IH and the effect of treatment. They observed only few and mild side effects.[21]

A multicenter retrospective analysis was carried out on 110 children by Price et al[13] in University of Miami in USA. They compared the efficacy and adverse effects of propranolol versus oral corticosteroids. They observed higher clearance rate with propranolol as compared to oral corticosteroids. (i.e., 82% versus 29%; P<.01). Adverse effects were fewer with propranolol whereas more frequent with oral corticosteroids. Subsequent surgical interventions were needed less often with propranolol therapy as compared to the oral corticosteroids.[13]

A study carried out by Xiao et al[12] also recommended that propranolol should now be used as a first line treatment in IHs when intervention is required.

The results of my study confirmed to the above-mentioned studies, in which propranolol was reported as a safe and efficacious treatment for IHs. The results of my study also confirmed to the comparative trials between oral propranolol and oral corticosteroids showing propranolol to be significantly superior to oral corticosteroids regarding its efficacy in treatment of IHs. The results of my study showed no significant side effects of both drugs again confirming to the results of most of above-mentioned studies except one. These meager differences can be attributed to the different genetic characteristics of the study population in my research. Furthermore, there is increasing awareness about prednisolone side effects in developed countries as compared to our setup.

This is the first local study carried out in Pakistan. In this research, the aim was to explore new horizons in the treatment of IHs. Because there is growing concern about the side effect profile of corticosteroids, propranolol was studied for efficacy and compared to corticosteroids. The therapeutic effects in both groups definitely persisted and sustained up to 1-month. However, to evaluate the long-term efficacy of propranolol, further prospective randomized controlled clinical trials with longer follow-up will be needed. In these trials, newer treatment modalities need to be explored, such as the combination of oral propranolol with oral corticosteroid and local injection of Bleomycin in combination with oral propranolol.

Conclusion

Propranolol had superior efficacy six weeks post-treatment, irrespective of the patient's age and gender. Hence, oral propranolol should be the preferred choice for treating infantile hemangioma.

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