Infantil Hemangioma and Optimum Dose of Propranolol Treatment: A Retrospective Tertiary-Center Study

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Abstract

Background/Objectives: Propranolol is the mainstay treatment of infantile hemangioma, and the optimal dose is unclear. Few studies are comparing the efficacy of propranolol dose of 2 vs.3 mg/kg/day. We compared the efficacy between these two doses and propranolol groups with no treatment group.

Methods: One hundred eight patients with infantile hemangioma (15 days-27 months of age) were examined. The patients with high-risk features and/or a score of >6 points are given propranolol with a final dose of 2 or 3 mg/kg/day according to tolerance for 6-12 months. The resolutions rates for propranolol vs. placebo and propranolol 2 mg/kg/day vs. 3 mg/kg/day are compared.

Results: The demographic and clinical features of the groups (the non-treatment, propranolol 2 mg/kg/day group, propranolol 3 mg/kg/day group) are similar. Propranolol is significantly efficent in infantil hemangioma treatment ($p<0.001$). The resolution rates are not statistically different between 2 mg/kg/day propranolol group vs 3 mg/kg/day propranolol group at the sixth (68,59 ± 28,95 vs 73,44 ± 32,54)($p=0,673$) and twelfth month ($p=0,673$) (89,08 ± 46,58 vs 91,13 ± 37,46 respectively)of follow up. A milld (n=3)(4%) adverse event was reported with no need for cessation.

Conclusions: Propranolol is a safe drug for treating infantile hemangioma with an ideal dose of 2 mg/kg/day rather than 3 mg/kg/day.

Introduction:

Infantil hemangioma is the most frequent benign tumor in infants (4%-5%). Half of the lesions spontaneously resolve in one year. Clear treatment indications are ulceration, functional impairment, disfigurement, life-threatening lesions (1). A score above six points on the infantile hemangioma severity scale is considered for treatment (2). Propranolol is used for treatment, and the dose range is 2-4 mg/kg/day, twice a day. The dose is escalated to 2 or 3 mg/kg/day in one-week intervals. However, the optimum dose of propranolol is not specific (3). This treatment duration is generally six months. Treatment is prolonged to one year in case of incomplete resolution (4). This study compares the resolution rates at the sixth and twelfth months of follow-up in the propranolol and non-propranolol groups. We also compare the resolution rates at the sixth and twelfth months between groups with two doses (2 mg/kg/day vs. 3 mg/kg/day).

Material-method:

One hundred eight patients (15 days, 27 months of age) with infantile hemangioma were included in this retrospective study. All of them are followed up for at least six months. In addition, the data between December 15, 2019, and December 15, 2019, was examined. This study is performed following the Declaration of Helsinki and Good Clinical Practice guidelines. In addition, the local ethics committee (both Ministry of Health, Osmangazi University Ethics comittee) approved this study. The study did not include patients with bronchospasm, asthma, hypoglycemia, hyperkalemia, bradycardia, congenital

hemangioma, Kasabach-Merritt, or PHACE (posterior fossa malformations, hemangiomas, arterial abnormalities, cardiac abnormalities, eye abnormalities, sternal cleft) syndrome.

Propranolol hydrochloride was administered for the patients with high-risk criteria. High-risk criteria were life-threatening lesions, ulceration, and risk of functional impairment. In addition, lesions in the periorbital, nasal, labial, laryngotracheal, and limb joints had a functional impact (4). Hemangioma severity scale was performed for all of the patients. A score above six points was considered for treatment regardless of high-risk features (5). Propranolol hydrochloride (oral solution or tablet) was started with a dose of 1 mg/kg/day and increased 1 mg/kg/day every one-week intervals up to 3 mg/kg/day. Electrocardiogram, echocardiogram, full blood count, serum glucose, ALT, AST, creatinine, urea, bilirubin were studied at the first week. The electrocardiogram, full blood count, serum glucose, ALT, AST, creatinine, urea, and bilirubin were repeated every visit, and the adverse events were documented. The drug was stopped in the cases with complete remissions after six months. To avoid rebound relapses, propranolol is escalated to half dose for one month before cessation. The treatment continued up to twelve months in case of incomplete resolution. At each visit, the size and depth of superficial and deep components, color intensity were documented. Resolution is the disappearance of infantile hemangioma. Ultrasonography was performed at diagnosis, sixth and or twelve months. Volume (width × height2 /2.1) is calculated by the width and height of the lesion written in the ultrasonography report (6). Resolution rates at the sixth and twelfth months were calculated for all patients.

Statistical analysis:

SPSS (Statistical Package for Social Sciences) 21.0 program for Windows was used for the data evaluation. Continuous variables were measured as mean+standard deviation. Response rates to propranolol was calculated by analysis of paired *t*-test, Anova, Ki-kare. A *P value* <0.05 is considered significant.

Results:

The patients (n=108) with infantile hemangioma were divided into three groups. These groups were the non-treatment group (n=33) and treatment groups (propranolol hydrochloride) receiving a recent total dose of 2 mg/kg/day (n=39) or 3 mg/kg/day (n=36). Out of 108 patients, 42 (38,8%) were male, 66 (61,2%) were female, 91 (84,3%) had localised infantile hemangioma, the lesion location was face in 73 (67,5%), 85 (78.7%) had a single lesion. The distribution of gender, presentaion, morphologic classification between these three groups were statistically similar. Mean age (months) at onset of hemangioma was 2,33 ± 2,41 in the non treatment group, 2,03 ± 1,82 in the group receiving 2 mg/kg/day propranolol and 3,69 ± 1,65 in propranolol group with a dose of 3 mg/kg/day (p=0,463). Mean age (months) at diagnosis, at start of treatment did not differ between these groups. Non-facial lesions are significantly more prevelant in the propranolol group (2 mg/kg/day) insidentally than the non-treatment group and propranolol group with a dose of 3 mg/kg/day (48.7% vs. 21.2% and 25% respectively) We

gave the final dose according to the tolerability, escalating dose 1 mg/kg/day every week. The groups with different doses of propranolol had similar risk factors.(Table 1).

Table 1
Demographic and clinical characteristics

	Non-treatment group	Treatment groups		p
		2 mg/kg/day, bid	3 mg/kg/day, bid	
Gender, (n,%) **Male/Female**	12(36,4) / 21(63,4)	14(35,9) / 25(64,1)	16 (38,9) / 20(61,1)	0,704
Mean age at onset of hemangioma, (months)	2,33 ± 2,41	2,03 ± 1,82	3,69 ± 1,65	0,463
Mean age at diagnosis, (months)	10,70 ± 12,28	6,26 ± 13,11	8,28 ± 11,68	0,284
Mean age at start of treatment, (months)	10,97 ± 16,24	8,92 ± 13,23	10,15 ± 14,45	0,739
Morphologic classification, (n,%)				
Localized (focal)	29 (87,9)	32 (82,1)	30 (83,3)	0,549
Segmental	4 (12,1)	3 (7,7)	3 (8,3)	0,776
Indeterminate	0 (0)	4 (10,3)	3 (8,3)	0,446
Primary location, (n,%)				
Facial	26 (78,8)	20 (51,3)	27 (75)	0,317
Non-facial	7 (21,2)	19 (48,7)	9 (25)	0,023
Presentation, (n,%)				
Single lesion	26 (78,7)	29 (74,4)	30 (16,7)	0,782
Multiple lesions	7 (21,2)	10 (25,6)	6 (83,3)	0,182

Bid: Divided twice daily

Only 21 (19,4%) of 108 patients had complete resolution at 6 months of follow-up. In the treatment groups (2 mg/kg/d, 3 mg/kg/d) and the non-treatment group, the resolution rates at sixth and twelft months of follow-up significantly differed (Table 2). Duration of propranolol treatment was 8,26 ± 12,33 months in the in the propranolol group (2 mg/kg/day) and 6,56 ± 10,53 months in the propranolol group (3 mg/kg/day) (p=0,773). The resolution rates were similar between these groups with two different doses of propranolol (2 mg/kg/day vs. 3 mg/kg/day) at the sixth and twelft month of follow-up (Table 3).

Table 2
Comparison of three treatment groups

	Non-treatment group	Treatment groups		p
		2 mg/kg/day, bid	3 mg/kg/day, bid	
Resolution rate, (%)				
At 6 months	35,76 ± 36,59	68,59 ± 28,95	73,44 ± 32,54	<0,001
At 12 months	51,52 ± 44,09	89,08 ± 46,58	91,13 ± 37,46	<0,001
Bid: Divided twice daily				

Table 3
Comparison of propranolol treatment groups

	Treatment groups		p
	2 mg/kg/day, bid	3 mg/kg/day, bid	
Duration of propranolol treatment (months)	8,26 ± 12,33	6,56 ± 10,53	0,773
Resolution rate, (%)			
At 6 months	68,59 ± 28,95	73,44 ± 32,54	0,673
At 12 months	89,08 ± 46,58	91,13 ± 37,46	0,673

Sleep disorder (n=2) (2.6%), and bronchiolitis (n=1)(1.3%) were documented side effects of propranolol and supportive treatment was given. These side effects were transient, treatment is not delayed or stopped in these patients.

Discussion:

Infantil hemangioma has tendancy for spontanous resolution. However, the patients with ulceration, impairment of vital function, disfigurement should be treated (7). Additionally, we added the hemangioma severity scale in decision making (1) With a score of 6 points is. The first line treatment is propranolol. A target dose of 2-3 mg/kg/gün is recommended. Infants (corrrected age>8 weeks, without comorbidity and with significant social support can be managed outpatient (7). According to a consensus statement, recommendation of propranolol dose is 1 or 2 mg/kg/day, bid (8). Begining with 1 mg/kg/day and escalating up to 3 mg/kg/day is possible. However; FDA approved a final dose of 3.4 mg/kg/day of propranolol hydrochlorur oral solution. However, optimal dose is not clear.Generally, treatment duration is 3-12 months (9). Generally 2 or 3 mg/kg/day final dose is used for the treatment of infantil hemangioma. The most common side effects (%10) are diarrhea and sleep disorders (10).We did not exceed the dose of 3 mg/kg/day. We report few transient adverse events, sleep order in two, bronchiolitis is one.

In a prospective randomised trial, of 456 patients, placebo (n=268) group was compared with propranolol group (3 mg/kg/day)(n=188). In six months, complete remission rate was significantly higher in the

propranolol group than the plasebo (60% vs. %4 respectively)(p<0.001). The rates of side effects did not differ between the groups (11). We similarly report that comparing with no drug group, the resolution rates are statistically higher in the propranolol groups.

In another trail, forty patients (age of 9 weeks-5 years) received a final dose of 2 mg/kg/day propranolol. In the third trial fourteen patients aged <16 weeks received prooranlol 3 mg/kg/day fifteen days and 4 mg/kg/day fifteen days. The data of these three trials revealed that, the risk of total remission of the lesionafter oral propranolol 1 mg/kg/day was 13.48 times that after plasebo, for 3 mg/kg/day, it was 16.61 times that after plasebo. Comparing the propranolol group and the plasebo group, there was no significant difference in the rates of adverse events (12).

Goto et al. reported that, of 54 infants, Group A (propranolol 2 mg/kg/day) was compared with Group B (propranolol 3 mg/kg/day) had similiar efficacy of resolution. A visual analog scale is used for detecting the color and size of the lesions. They recommend 2 mg/kg/day final dose for infantile hemangioma (13).

Conclusions:

Propranolol is safe in infantil hemangioma treatmentç Propranolol's efficacy is well established comparing with plasebo in infantil hemangioma. There are few studies comparing the dose of 2 mg/kg/day versus 3 mg/kg/day propranolol's efficacy and side effects in infantil hemangioma. A final dose of 2 mg/kg/day of propnalolol is optimal.

Declarations

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Informed Consent: Written informed consent was obtained from all participants.

There is no conflict of interest between the authors.3

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