HK J Paediatr (new series) 2023;**28**:228-233

Original Article

Infantile Haemangioma and Optimum Dose of Propranolol Treatment: A Retrospective Tertiary Centre Study

HM ***Cakmak***, O ***Kartal***

Abstract

Purpose: Propranolol is the mainstay treatment of infantile haemangioma, and the optimal dose is unclear. The propranolol treatment protocol has not been standardised. This study aims to compare the efficacy of medium-dose propranolol (2 mg/kg/day) and high-dose propranolol (3 mg/kg/day). **Methods:** In this retrospective non-randomised series study (n=108) (15 days, 27 months of age), we designed three groups, no treatment (n=33), propranolol 2 mg/kg/day (n=39) and propranolol 3 mg/kg/day (n=36). The patients with high-risk features and a score of >6 points received propranolol with a random final dose of 2 or 3 mg/kg/day for 6 or 12 months. The patients were followed for up to twelve months, and their resolution rates were calculated using ultrasonographic volume changes. **Findings:** The demographics and clinical features of the groups (no-treatment, propranolol 2 mg/kg/day, propranolol 3 mg/kg/day) were similar. Propranolol (2 mg/kg/day and 3 mg/kg/day) treatment achieved significantly more resolution than no treatment group ($p<0.001$). Comparing propranolol 2 mg/kg/day and 3 mg/kg/day groups, we found the resolution rates similar (68.59 ± 28.95 vs 73.44 ± 32.54)($p=0.673$) and twelfth months (89.08 ± 46.58 vs 91.13 ± 37.46 respectively) ($p=0.673$) of follow up. Mild (n=3) (4%) adverse events were managed with no cessation. We stopped the treatment in one patient with an atrioventricular block. **Conclusions:** Propranolol is a safe drug for treating infantile haemangioma. The treatment regimen with a propranolol dose of 3 mg/kg per day has the same resolution rate as the 2 mg/kg regimen. Therefore, 2 mg/kg/day is a good option for infantile haemangioma.

Key words *Capillary haemangioma; Propranolol hydrochloride*

Introduction

Infantile haemangioma is infants' most frequent benign tumour (4-5%). Half of the lesions spontaneously resolve in one year. Treatment indications are ulceration, functional impairment, disfigurement, and life-threatening lesions.[1] Patients with an infantile haemangioma severity scale score above six points are considered for treatment.[2] Food and Drug Administration approved oral propranolol, a nonselective adrenergic receptor-blocking agent, in 2014 for infantile haemangioma treatment. The total daily doses vary between 2-4 mg/kg. The therapy begins with 1 mg/kg/day for one week, and the dose is escalated to 2 or 3 mg/kg/day in the following weeks. However, the guidelines recommend different final total daily doses.[3] This treatment duration is generally six months and prolonged to one year in incomplete resolution.[4] This study compared the resolution rates at the sixth and twelfth months of follow-up between propranolol 2 mg/kg/day, propranolol 3 mg/kg/day, and no treatment groups.

Eskisehir City Hospital, Department of Pediatric Hematology-Oncology, Eskisehir, Turkey
HM **Cakmak** *MD*

Gulhane Research and Training Hospital, Department of Pediatric Hematology-Oncology, Ankara/Turkey
O **Kartal** *MD*

Correspondence to: Dr HM **Cakmak**
Email: h.m.tokuc@hotmail.com

Received June 21, 2022

Methods

This retrospective study included one hundred eight patients (15 days, 27 months of age) with infantile haemangioma. All of them were followed up between six to twelve months. In addition, the data between 15 December 2019 and 15 December 2021 was examined. This non-randomised study is performed following the Declaration of Helsinki and Good Clinical Practice guidelines. In addition, the local ethics committee approved this study (Date: 02.03.2021, no:08). The exclusion criteria included patients with bronchospasm, asthma, hypoglycaemia, hyperkalaemia, bradycardia, congenital haemangioma, Kasabach-Merritt, or PHACE (posterior fossa malformations, haemangiomas, arterial abnormalities, cardiac abnormalities, eye abnormalities, sternal cleft) syndrome. The diagnosis was made by physical examination. We performed an ultrasound again for confirmation in several cases with an equivocal diagnosis.

The urgent propranolol treatment indications have one high-risk criterion: life-threatening lesions, ulceration, and risk of functional impairment. In addition, some regions are essential for treatment. These are periorbital, nasal, labial, laryngotracheal, and limb joints.[4] We also began for cosmetic reasons or anxious parents.

We performed a haemangioma severity scale for all of the patients. A score above six points was considered for treatment regardless of high-risk features (Table 1).[5]

The recommended treatment dose for infantile haemangioma is 2-4 mg/kg/day.[6] One mg/kg/day dose was the beginning dose to check the patient's tolerance to propranolol treatment, and it lasted for only one week in every patient. After one week, the dose was increased to 2 mg/kg/day. In the second week of the treatment, some received 2 mg/kg/day; the others received 3 mg/kg/day for at least six months. Therefore, a final dose of 3 mg/kg/day is recommended in the prescription of propranolol hydrochloride syrup.[7] We compared the efficacy of different propranolol regimens (propranolol 2 or 3 mg/kg/day divided into two doses for 6 to 12 months). We decided on the final doses according to the tolerability.

The electrocardiogram, whole blood count, serum glucose, ALT, AST, creatinine, urea, and bilirubin were repeated every visit, and we have documented the adverse events. In addition, we recorded the colour intensity, size, and depth of both superficial and deep lesions at each visit. Ultrasonography was performed at diagnosis, sixth and or twelve months after commencement of treatment.

Table 1 Haemangioma severity scale

Clinical characters	Score	Category subscore
Size (widest diameter, face, and ear)		
<1 cm	1	
>1 cm, ≤5 cm	2	
>5 cm, ≤10 cm	3	
>10 cm, ≤20 cm	4	
>20 cm	5	
Size (widest diameter, head, and neck)		
≤5 cm	1	
>5 cm, ≤15 cm	2	
>15 cm	3	
Mucose membrane (except limb)	1	
Extremities and trunk (except)	1	
Chest	2	
Perineal, perianal, genital	3	
Lumbosacral	2	
Head and neck	2	
Peripheral face	3	
Central face (except limb, nose tip, eye circle)	5	
Ear, limb, nose, eye circle	6	
Associated anomalies		
Face localisation with a diameter >5 cm	6	
The midline of the lumbosacral vertebra with a diameter ≥2.5 cm	5	
Segmental at perineal, perianal, genital	5	
Complications		
Bacterial infections	1	
Ulceration	2	
Feeding difficulty	2	
Torticollis	2	
Cartilage abnormality	3	
Airway involvement	3	
Blurred vision	3	
Hypothyroidism	2	
Anaemia	2	
Hearth failure	2	
Gastrointestinal bleeding	2	
Liver failure	2	
Pain		
Mild, moderate, without the need for systemic treatment	1	
Moderate and requiring oral analgesic	2	
Severe with the need for opiates	3	
Severe with the need for hospitalisation	4	
Disfigurement (face and ear)		
Minimal change ± telengiectasia	2	
Fibrotic scar	3	
Anatomic deformity	4	
Disfigurement (head and neck)		
Minimal change ± telengiectasia	0	
Fibrotic scar	1	
Anatomic deformity	2	

Resolution is defined as the disappearance of infantile haemangioma. We calculated resolution rates for all patients. First, volume (width × height 2/2.1) was calculated by the width and height of the lesion as described in the ultrasonography report.[8] Then, we compared the changes before and after therapy and yielded the resolution rates (first volume-last volume/first volume).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) 21.0 program for Windows was used for the data evaluation. We measured continuous variables as mean standard deviation. We calculated response rates using paired t-tests, ANOVA, and Ki-kare. A p-value <0.05 is considered significant.

Results

The patients (n=108) with infantile haemangioma were divided into three groups. The nontreatment group (n=33) and treatment groups (propranolol hydrochloride) received a final 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, and 91 (84.3%) had localised infantile haemangioma. The majority of the lesions [73/108 (67.5%)] were found on the face, and most [85/108 (78.7%)] had a single lesion. The gender, presentation, and morphologic classification distribution between these three groups were statistically similar. Mean age (months) at onset of haemangioma was 2.33 ± 2.41 in the no-treatment group, 2.03 ± 1.82 in the 2 mg/kg/day propranolol group and 3.69 ± 1.65 in 3 mg/kg/day propranolol group (p=0.463). Non-facial lesions are significantly more prevalent in the 2 mg/kg/day propranolol group than in the nontreatment group and 3 mg/kg/day propranolol group (48.7% vs 21.2% and 25% respectively) (p=0.023). Demographics and baseline characteristics were similar across the study groups (no treatment, propranolol 2 mg/kg/day, propranolol 3 mg/kg/day) (Table 2).

Only 21 (19.4%) of 108 patients' lesions disappeared within six months of follow-up. Within the sixth and twelfth months of follow-up, the resolution rates significantly differed in the treatment (2 mg/kg/d, 3 mg/kg/d) and the nontreatment groups (Table 3). Duration of propranolol treatment was 8.26 ± 12.33 months in the 2 mg/kg/day propranolol group and 6.56 ± 10.53 months in the 3 mg/kg/day propranolol group (p=0.773). The resolution rates were similar between 2 mg/kg/day and 3 mg/kg/day propranolol groups at the sixth and twelfth months of follow-up (Table 4). Only two relapsed after the cessation of propranolol. During treatment, sleep disorder (n=2) (2.6%), bronchiolitis (n=1) (1.3%), second-degree atrioventricular block (n=1) (1.3%) occurred. None had hypotension, hypoglycaemia, or diarrhoea. Sleep disorder and bronchiolitis were transient; treatment was not interrupted in these patients. We stopped the treatment in a patient with a second-degree atrioventricular block.

Discussion

Infantile haemangioma has tendancy for spontanous resolution. However, the potential for impaired organ function and disfigurement should be treated for patients with ulcerated lesions. Patients scoring >6 on the haemangioma severity scale also qualify for medical treatment.[1] Additionally, we added the haemangioma severity scale in decision-making. The first-line treatment is propranolol. Infants (corrected age >eight weeks, without comorbidity and significant social support) can be managed outpatient.[9] A systematic review reported that oral propranolol effectively induces complete clearance of infantile haemangioma. The adverse risks did not significantly increase in the propranolol group.[10]

In a network meta-analysis of 18 randomised trials in infantile haemangioma, oral propranolol with doses ranging from 1 to 4 mg/kg per day has the most significant mean of expected clearance compared with oral corticosteroids and placebo.[11] According to a consensus statement on managing infantile haemangiomas, the recommendation of propranolol dose is 1 or 2 mg/kg/day, bid.[12] Beginning with 1 mg/kg/day and escalating to 3 mg/kg/day is possible. However, the FDA approved a final dose of 3 mg/kg/day of propranolol hydrochloride oral solution. However, the last total dose still needs to be discovered. Generally, treatment duration is 3-12 months, and the final dose of 2 or 3 mg/kg/day treats infantile haemangioma.[6-13]

Here, we report a series of one hundred-eight patients with infantile haemangioma. It consisted of nontreatment and treatment groups with a final propranolol dose of 2 or 3 mg/kg/day. They had similar clinical features and demographic characteristics. However, complete

resolution rates were significantly higher in the propranolol groups (2 and 3 mg/kg/d) compared with the nontreatment group ($p<0.001$) at both six months and twelve months of follow-up.

In a prospective randomised trial of 456 patients, the placebo (n=268) group was compared with the propranolol group (3 mg/kg/day)(n=188). In six months, the complete remission rate was significantly higher in the propranolol group than in the placebo (60% vs 4% respectively) ($p<0.001$). The rates of side effects did not differ between the groups.[14] We report that the resolution rates are statistically higher in the propranolol 2 mg/kg/day and 3 mg/kg/day groups at the sixth and twelfth months of follow-up compared with the no-treatment group. Our results support that propranolol is an effective drug for infantile haemangioma.

Table 2 Demographic and clinical characteristics

	Nontreatment Group (n=33)	**Treatment Groups**		**p**
		2 mg/kg/day, bid (Divided twice daily)(n=39)	**3 mg/kg/day, bid (Divided twice daily)(n=36)**	
Gender, (n) (%)				
Male/Female	12 (36.4) / 21 (63.4)	14 (35.9) / 25 (64.1)	16 (44.4) / 20 (55.6)	0.704
Age at onset of haemangioma (months) (Mean ± standard deviation)	2.33±2.41	2.03±1.82	3.69±1.65	0.463
Age at diagnosis (months) (Mean ± standard deviation)	10.70±12.28	6.26±13.11	8.28±11.68	0.284
Morphologic classification (n) (%)				
Localised (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

Table 3 Comparison of the resolution rates between the nontreatment group and the treatment groups

Resolution rate (%)	**Nontreatment Group**	**Treatment Groups**		**p**
		2 mg/kg/day, bid (Divided twice daily)	**3 mg/kg/day, bid (Divided twice daily)**	
In the 6th month	35.76±36.59	68.59± 28.95	73.44±32.54	0.001
In the 12th month	51.52±44.09	89.08±46.58	91.13±37.46	0.001

Table 4 Comparison of the resolution rates between the treatment groups with different doses

	Treatment Groups		**p**
	2 mg/kg/day, bid (Divided twice daily)	**3 mg/kg/day, bid (Divided twice daily)**	
Duration of propranolol treatment (months)	8.26±12.33	6.56±10.53	0.773
Resolution rate (%)			
In the 6th month	68.59±28.95	73.44±32.54	0.673
In the 12th month	89.08±46.58	91.13±37.46	0.673

In another trial, 40 patients (9 weeks-5 years) received a final dose of 2 mg/kg/day of propranolol. In the third trial, fourteen patients aged <16 weeks received propranolol 3 mg/kg/day and 4 mg/kg/day for fifteen days. The data of all three trials revealed that the lesion's chance of complete remission rate after oral propranolol 1 mg/kg/day was 13.48 times better than placebo. For 3 mg/kg/day, it was 16.61 times better than a placebo. The adverse events were not significantly different when comparing the propranolol (2 mg/kg/day and 3 mg/kg/day) groups.[15]

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) and had similar efficacy. We used a visual analogue scale to detect the lesions' colour and size. Therefore, they recommended the final dose of 2 mg/kg/day for infantile haemangioma.[16] We also used the haemangioma severity scale adopted from Léauté-Labrèze.[2] Patients with high scores (≥6) are also candidates for treatment.

Propranolol hydrochloride oral solution has a target dose of 3 mg/kg/day, escalating to 1 mg/kg/day weekly.[7] In our study, some patients are given a final dose of 2 mg/kg/day or 3 mg/kg/day. The distribution of the patients into the groups is random. Our study found that complete resolution rates at the sixth and twelfth months of follow-up were similar between the propranolol 2 mg/kg/day and 3 mg/kg/day groups. Therefore, 2 mg/kg/day is appropriate for infantile haemangioma treatment.

The most common side effects (10%) of propranolol are bronchiolitis (8-13%) and sleep disorders (infants 16-18%).[7] In addition, cold extremity, gastrointestinal side effects, agitation, irritability (1-10%), and second-degree atrioventricular block (<1%) are also reported side effects.[17] Our cohort reports a few transient adverse events, two with sleep disorder (2.6%) and one with bronchiolitis (1.3%). Furthermore, one patient (1.3%) developed an atrioventricular block requiring withdrawal of the propranolol treatment. We report that our patients had a lower rate of bronchiolitis and sleep disorders and a relatively more common second-degree atrioventricular block than reported previously.

The target doses of propranolol in the current guidelines differ. The American experts agree to treat infantile haemangioma with a propranolol dose of 2-3 mg/kg daily. However, the Spanish policies and Australasian guidelines point to different target doses (3 mg/kg per day and a maximum dose of 1-2 mg/kg daily). Also, the guidelines need to mention the ideal time to begin treatment. Increasing amounts of propranolol cause elevated rates of adverse events, which may increase the need for a lower effective dose.[18]

A meta-analysis comparing the data of randomised control trials (RCT) and nonrandomised control (non-RCT) trials suggests that a 2 mg/kg/day dose is a good choice for infantile haemangioma.[17] Comparing RCT with non-RCT groups, bias assessment found a low risk of bias. Previous studies support our results. However, some limitations could be addressed in our research. One of these limitations is the retrospective setting and difference in the meantime for diagnosis between the groups. However, this difference did not meet a statistical significance. In addition, the ideal time to begin treatment should be mentioned in the guidelines.

Conclusions

Propranolol is safe for infantile haemangioma. Its efficacy is well established compared with placebo in infantile haemangioma. However, few studies compare the effectiveness and side effects of the dose of 2 mg/kg/day versus 3 mg/kg/day of propranolol. Therefore, 2 mg/kg/day of propranolol is as effective as 3 mg/kg/day for patients with infantile haemangioma.

Conflicts of Interest

All authors have disclosed no conflicts of interest.

References

1. Mull JL, Chamlin SL, Lai JS, et al. Utility of the Hemangioma Severity Scale as a Triage Tool and Predictor of Need for Treatment. Pediatr Dermatol 2017;34:78-83.
2. Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: part II. Risks, complications and treatment. J Eur Acad Dermatol Venereol 2011;25:1254-60.
3. Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. Lancet 2017;390:85-94.
4. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomised, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015;372:735-46.
5. Baselga E, Dembowska-Baginska B, Przewratil P, et al. Efficacy of Propranolol Between 6 and 12 Months of Age in High-Risk Infantile Hemangioma. Paediatrics 2018;142:e20173866.
6. Darrow DH, Greene AK, Mancini AJ, Nopper AJ; SECTION ON DERMATOLOGY, SECTION ON OTOLARYNGOLOGY–HEAD AND NECK SURGERY, and SECTION ON PLASTIC SURGERY. Diagnosis and Management of Infantile Hemangioma. Paediatrics 2015;136:e1060-104.

7. Hemangeol [Prescribing information]. Parrispanny NJ. Pierre Pharmaceuticals Inc. August 2021
8. Zhang L, Wu HW, Yuan W, Zheng JW. Propranolol therapy for infantile hemangioma: our experience. Drug Des Devel Ther 2017;11:1401-8.
9. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Paediatrics 2013;131:128-40.
10. Novoa M, Baselga E, Beltran S, et al. Interventions for infantile haemangiomas of the skin. Cochrane Database Syst Rev 2018;4:CD006545.
11. Chinnadurai S, Fonnesbeck C, Snyder KM, et al. Pharmacologic Interventions for Infantile Hemangioma: A Meta-analysis. Paediatrics 2016;137:e20153896.
12. Smithson SL, Rademaker M, Adams S, et al. Consensus statement for the treatment of infantile haemangiomas with propranolol. Australas J Dermatol 2017;58:155-9.
13. Hoeger PH, Harper JI, Baselga E, et al. Treatment of infantile haemangiomas: recommendations of a European expert group. Eur J Pediatr 2015;174:855-65.
14. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomised, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med 2015;372:735-46.
15. Novoa M, Baselga E, Beltran S, et al. Interventions for infantile haemangiomas of the skin: abridged Cochrane systematic review and GRADE assessments. Br J Dermatol 2019; 180:527-33.
16. Goto K, Ozeki M, Yasue S, Endo S, Fukao T. A retrospective study of 2 or 3 mg/kg/day propranolol for infantile hemangioma. Pediatr Int 2020;62:751-3.
17. Yang H, Hu DL, Shu Q, Guo XD. Efficacy and adverse effects of oral propranolol in infantile hemangioma: a meta-analysis of comparative studies. World J Pediatr 2019;15:546-58.
18. Tan X, Guo S, Wang C. Propranolol in the Treatment of Infantile Hemangiomas. Clin Cosmet Investig Dermatol 2021;14:1155-63