

Propranolol as a First-Line Treatment of Infantile Hemangioma: Single Center Experience

İnfanıl Hemanjiyomun Birinci Sıra Tedavisinde Propranolol: Tek Merkez Deneyimi

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ABSTRACT Objective: Infantile hemangiomas (IHs) are the most common benign vascular tumors in infancy. Spontaneous regression is expected in majority of IHs, so watchful waiting is the best management. Currently propranolol has taken the place of corticosteroids for the treatment of risky IHs. Herein we aimed to analyze our patients with IHs treated with propranolol. **Material and Methods:** There were 240 patients with diagnosis of IH, treatment was indicated in 11.3% (n:27) of them, and these 27 patients received propranolol as a first-line treatment between January 2012-January 2015. Medical records of these 27 patients were analyzed retrospectively. Clinical characteristics, physical examination findings, treatment indications, treatment details, responses and side effects of propranolol were analyzed retrospectively. **Results:** The median age at diagnosis was 3 months (1-15), and M/F ratio was 0.23. The most common hemangioma localization was skin and head-neck region in 55.6% of patients. Treatment indications were local complications (haemorrhage, ulceration, infection) (44.4%), life threatening organ dysfunction (33.3%) and relative indications (22.2%). The median follow-up period was 12 months (1-26 months). Pallor and partially regression in hemangiomas were observed between the fourth and sixth weeks in all patients. Complete remission occurred in 15 patients, treatment is going on with partial remission in remaining 12 cases. There was no observed side effects of propranolol. **Conclusion:** Propranolol is a well-tolerated, efficacious, and safe drug for treatment of IHs. It can be initiated and administered in the outpatient setting. Treatment indications of IHs may become more flexible taking into account of the safety profile of propranolol.

Key Words: Hemangioma, capillary infantile; propranolol; treatment outcome

ÖZET Amaç: İnfantil hemanjiyomlar (İH) süt çocukluğu döneminin en sık karşılaşılan benign vasküler tümörleridir. Bu hastaların büyük bölümünde kendiliğinden gerileme beklenmektedir ve bu nedenle izleyerek beklemek en iyi yaklaşımdır. Günümüzde riskli İH tedavisinde kortikosteroidlerin yerini propranolol tedavisi almıştır. Biz burada İH tanısıyla izlediğimiz propranolol tedavisi uyguladığımız hastaları analiz ettik. **Gereç ve Yöntemler:** Ocak 2012-Ocak 2015 tarihleri arasında İH tanısı almış 240 hasta vardı, bunların %11,3 (n:27)'üne tedavi endikasyonu konmuştu ve ilk sıra tedavide propranolol verilmişti. Bu 27 hastanın tıbbi kayıtları retrospektif olarak incelendi. Klinik karakteristikler, fizik inceleme bulguları, tedavi endikasyonları, tedavi detayları, yanıtlar ve propranolol yan etkileri analiz edildi. **Bulgular:** Hastaların ortanca tanı yaşı 3 ay (1-15), E/K oranı 0,23 bulundu. Hemanjiyomun en sık lokalizasyonu deri ve baş boyun bölgesiydi (%55,6). Tedavi endikasyonları lokal komplikasyonlar (hemoraji, ülserasyon, enfeksiyon) (%44,4), hayatı tehdit eden organ disfonksiyonu (%33,3) ve göreceli endikasyonlar (%22,2) idi. Ortanca izlem süresi 12 aydı (1-26 ay). Tüm hastalarda lezyonda soluklaşma ve kısmi regresyon tedavinin 4-6. haftalarında gözlenmişti. Onbeş hastada tam gerileme izlenmişti, geriye kalan 12 hastada kısmi gerileme vardı ve tedavi devam etmekteydi. Hastaların hiçbirinde propranolol ilişkili yan etki izlenmedi. **Sonuç:** Propranolol, İH tedavisinde iyi tolere edilen, etkin ve güvenli bir ilaçtır. Propranolol ayaktan tedavide başlanabilen ve uygulanabilen bir ilaçtır. Propranololün güvenli bir uygulama profilinin olması İH tedavi endikasyonlarının daha esnek tutulması sağlamaktadır.

Anahtar Kelimeler: Hemanjiyom, infanıl kapiller; propranolol; tedavi sonucu

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Infantile hemangiomas are the most common benign vascular tumors in infancy, affecting 5-10% of the population.¹⁻³ Two major subgroups of vascular tumors are infantile hemangioma (IH) and congenital hemangioma (CH).^{4,5} Females (F) are affected more often than males (M), with M/F ratio of 1:3. Infants with hemangiomas had been reported in female sex, white (non-Hispanic), premature, of low birth weight, a product of multiple gestation, or born to mothers with advanced maternal age. The most common location of hemangiomas was skin with preference of head and neck region.^{1,3,6,7} Infantile hemangioma typically present shortly after birth and clinical course consists of three consecutive periods.⁸ Firstly enlargement of lesion occurs during proliferation phase, and it takes about 12 months. Spontaneous regression occurs in following involution period and it takes several years. Residual changes occur at the third phase such as telangiectasias, skin discoloration, and atrophic wrinkling.

Spontaneous regression is expected in majority of hemangiomas, so watchful waiting without any medical intervention is the best management. However medical treatment is needed in approximately 10% to 20% of cases. Presence of serious complications such as obstruction of airway, impairment of vision, gastrointestinal bleeding, ulcerations, infections and hemorrhage necessitate medical treatment.⁸⁻¹⁰ Corticosteroids have been the mainstay of treatment for hemangiomas, however they have many potential side effects and rebound growth does occur upon cessation of corticosteroid treatment.^{9,10} Interferon- α -2a (IFN α 2a) and vincristine are other second line agents that can be used in treatment of hemangioma even though their potentially serious side effects. Currently propranolol has taken the place of corticosteroids and it is recommended as first-line treatment of infantile hemangiomas.¹¹⁻¹⁷ In this study we present our successful treatment experience with oral propranolol in patients with hemangioma.

MATERIAL AND METHODS

Our aim is to analyze our patients with hemangioma treated with propranolol at the Dr. Behcet

Uz Children's Hospital Pediatric Hematology Oncology Clinic between January 2012 and January 2015. The safety and efficacy of propranolol therapy as administered according to protocol of Dr. Behcet Uz Children's Hospital were evaluated. Patients with ongoing or previous corticosteroid therapy were excluded. Medical records of patients were analyzed retrospectively. The characteristics of patients (age at diagnosis, sex, history of prematurity, low birth weight, and a product of multiple gestation, history of hemangioma), physical examination findings and characteristics of hemangioma (anatomic location, size, configuration, and presence of hemorrhage, ulceration, infection), treatment indications, treatment details and responses were obtained from the patients' files.

Medical diagnosis was done according to the medical history of a patient and physical examination findings in all cases. Vascular lesions were classified according to the International Society Study of Vasculer Anomalies (ISSVA) classification system.¹⁸ Periorbital hemangiomas have been followed up with colloboration of ophthalmology department. Abdominal ultrasonography has been performed in patients who had multiple skin hemangiomas, disseminated hemangiomatosis and abdominal magnetic resonance imaging has been done if necessary.

Propranolol treatment was given to hemangioma patients with impaired functional or cosmetic outcome if left untreated, and with complicated hemangiomas. Other than propranolol no other therapy for hemangioma was given. Contraindications for use of propranolol were defined as history or risk of asthma, reactive airway disease, impaired renal function, heart defects and arrhythmia/dysrhythmia with contraindication for the use of beta-blockers, central nervous system disease.

Hemangiomas have been treated by a standardized protocol using propranolol in our clinic and it has been initiated in the outpatient setting for all patients. Propranolol was given at a starting dose of 1 mg/kg/day, in two divided doses, and titrated to a dose of 2 mg/kg/day according to response within 1 to 4 weeks. The dose of propra-

nolol was adjusted to weight during follow-up visits. Syrup form of propranolol is not available in Turkey. So we used tablet form of propranolol. Propranolol tablet was dissolved in water which was boiled and than iced tap water, for each usage. The dose of a drug to be given to infants was calculated by this method. Parents were educated about preparation of propranolol solution. Also, parents were informed about possible symptomatic hypoglycemia, hypotension, bradycardia and educated to look for signs of poor perfusion, lethargy, loss of consciousness, poor feeding, wheezing, and respiratory distress.

A baseline complete blood count (CBC), serum blood glucose and potassium levels were analyzed for all patients before starting the propranolol treatment. All patients underwent full physical examination prior to initiating the propranolol treatment, which included cardiac examination, heart rate and blood pressure measurements, a 12-lead electrocardiogram, and echocardiogram. Follow-up visits were performed after the first week, the first month and every month thereafter. Monitoring protocol during the propranolol treatment was summarized in (Table 1). Digital photography was taken at each visit.

The duration of propranolol therapy is decided according to the clinical response. Propranolol treatment was continued until complete involution was achieved. Regression and/or cessation at growth of hemangioma were considered as positive response. Data were analyzed using SPSS 15.0 statistics software package and descriptive analysis was performed. For this study, ethical committee approval was taken and it conforms with the 2008 Helsinki Declaration principles.

RESULTS

There were 240 patients with diagnosis of hemangioma and 27 (11.3%) of them received propranolol as a first-line treatment between January 2012 and January 2015. Medical records of eligible 27 patients with infantile hemangioma were analyzed retrospectively. The median age at diagnosis was 3 months (1-15), and male to female ratio was 0.23.

TABLE 1: Monitoring protocol of propranolol treatment that is used at Dr. Behcet Uz Children Hospital.

Time	Evaluation
At the beginning of propranolol treatment	Physical examination, Heart rate ^α and blood pressure ^β measurements Complete blood count, Serum glucose* and potassium [†] levels, 12-lead electrocardiogram, Echocardiogram.
Every day of the first week of propranolol treatment	Fingerstick blood glucose* level
Monthly follow-up visits, after the first month of propranolol treatment	Physical examination, Heart rate ^α and blood pressure ^β measurements Serum glucose* and potassium [†] levels, 12-lead electrocardiogram

*:Hypoglycemia: serum blood glucose level < 70 mg/dL

†:Hypokalemia: serum blood potassium level < 2,5 mEq/L

α: Bradycardia was defined as a heart rate less than the second percentile for age.²⁵

β: Hypotension was defined according to the Pediatric Advanced Life Support Guidelines.²⁶

There were 10 patients ≤2 months of age. There was 1 patient with history of prematurity never more no other patient with low birth weight, in-vitro fertilization or a product of multiple gestation. Any patients had parental consanguinity and family history for hemangioma. Two patients had disseminated hemangiomatosis at birth (Figure 1). Characteristics of patients and hemangiomas, and also treatment details were summarized in Table 2. The most common hemangioma localization was skin and head-neck region in 55.6% of patients. Patients with two or more hemangiomas constituted 16% of all patients (n:4).

Treatment indications were local complications (haemorrhage, ulceration, infection) in 44.4%, life threatening organ dysfunction in 33.3% and relative indications in 22.2% of patients. Patients with complicated hemangioma (haemorrhage, ulceration, infection) received local wound care and antibiotic (topical and peroral) treatments in addition to propranolol. Mupirocin and amoxicillin clavulanate were topical and systemic antibiotic choices, respectively. Periorbital hemangiomas were managed and followed up with collaboration

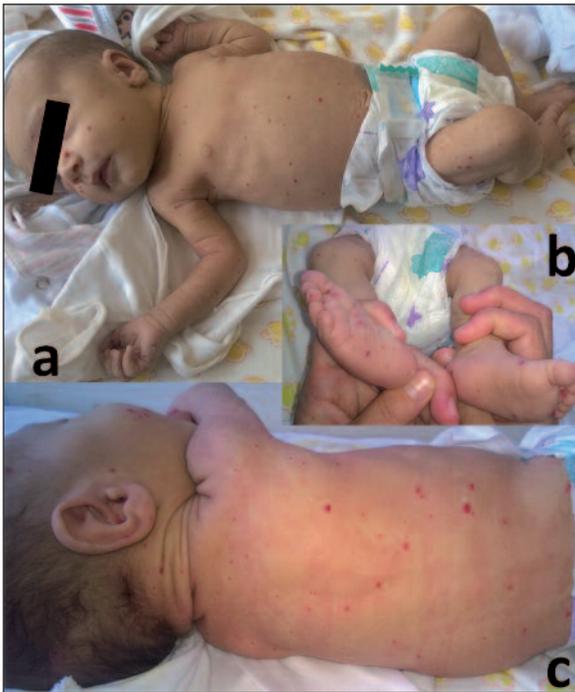


FIGURE 1a-c: (Patient number 26) A two months old girl with diagnosis of disseminated hemangiomatosis. She has multiple millimetric hemangiomas on her skin, through the body including palms and footpad. Also she has hemangiomas in her liver, and spleen. Her treatment with propranolol is going on.

of ophthalmologists, one patient with outer ear chanel hemangioma and other who had nasal hemangioma was followed up with otorhinolaryngologist. The median follow-up period was 12 (1-26) months. Pallor and partially regression in hemangiomas were observed between the fourth and sixth weeks in all patients. Treatment is on going in 12 cases. This group median follow-up was 5.5 months (1-9). Propranolol treatment was completed in 15 (55.5%) patients with complete involution and minimal residue. Recurrence was not observed after termination of treatment. The median duration of propranolol treatment was 12 (6-20) months. Photography of some selected cases are shown in figures 2 and 3. There was no side effects of propranolol observed.

DISCUSSION

Infantile hemangiomas are the most common benign vascular tumors of infancy and childhood. Hemangiomas affect 1-2.6% of newborns and 10-12% infants younger than 1 year old. Hemangiomas are

pale and pink macular similar to telangiectatic lesions at birth and firstly enlargement of hemangioma occurs during proliferation phase that takes about 12 months.^{1-5,8} Hemangiomas are usually diagnosed in the first 3 months of life. It is more common in girls and usually occurs in skin with preference of head and neck region.^{5,6,8} In our study, the median age at diagnosis was 3 months (1-15), male to female ratio was 0.23 and most common hemangioma localization was skin and head-neck region in 55.6% of patients, these results are consistent with the literature.^{1-3,5,6} Also in this study gestational age of one (4%) patient was <37 weeks and there was no other patient with low birth weight, in vitro fertilization or a product of multiple gestation. In the literature it has been reported that hemangiomas were more commonly seen in patients who were born prematurely, with low birth weight, in vitro fertilization or a product of multiple gestation.^{1,3,6,7}

Hemangioma is an entity often associated with spontaneous regression so watchful waiting without any medical intervention is the best management. However medical treatment is needed in approximately 10% to 20% of cases. Presence of serious complications such as obstruction of airway, impairment of vision, gastrointestinal bleeding, ulcerations, infections and hemorrhage necessitate medical treatment.⁹⁻¹¹ In this study, we used propranolol for 11.3% of patients and treatment indications were local complications (haemorrhage, ulceration, infection) in 44.4%, life threatening organ dysfunction in 33.3%, and relative indications in 22.2% of patients.

Corticosteroids (CS) had been used as the first-line treatment for hemangiomas during the last 40-45 years. Usually CS had been given by peroral administration, in addition to intralesional usage for periorbital hemangiomas. Efficacy of CS treatment was confirmed with many clinical studies.⁵⁻¹⁰ Dramatic responses in hemangiomas have been shown by CS therapy especially during proliferative phase, even though rebound growth might be seen in some hemangiomas after cessation of CS therapy. However, corticosteroids have many potential harmful side effects including increased risk for

TABLE 2: Clinical characteristics of patients.

Patient no.	Gender	Age at diagnosis and treatment (months)	Localization of hemangioma	Indications of treatment	Duration of propranolol treatment (months)
1	M	2	Left upper eyelid and left forehead	Risk of amblyopia	12
2	F	6	Left lower eyelid	Risk of amblyopia	9*
3	F	4	Right periorbital region and cheek	Risk of amblyopia	13
4	F	4	Upper lip	Haemorrhage and difficulties in feeding	18
5	F	2	Lower lip	Haemorrhage and difficulties in feeding	18
6	F	3	Left periauricular, cheek	Obstruction of outer ear way	18
7	M	2	Nose	Respiratuar tract obstruction	26
8	F	6	Nose	Respiratuar tract obstruction	6*
9	M	4	Tip of the nose	Relative (Cosmetic)	2*
10	F	1.5	Root of the nose, glabella	Risk of amblyopia	2*
11	F	5	Behind of left ear	Recurrent infection and ulceration	13
12	F	4	Behind of right ear, neck	Relative (Cosmetic)	26
13	F	6	Back of the neck	Relative	18
14	F	6	Back of the neck	Relative	12
15	F	3	Neck, chest, extremity	Relative	13
16	F	1	Left arm	Relative (Cosmetic)	23
17	M	8	Left arm	Recurrent infection and ulceration	18
18	F	6	Left hand	Recurrent haemorrhage and ulceration	12
19	F	1	Left upper extremity	Recurrent haemorrhage and ulceration	8*
20	F	1	Axillary and shoulder	Recurrent haemorrhage and ulceration	3*
21	M	2	Axillary	Recurrent haemorrhage and ulceration	2*
22	F	5	Left thigh	Recurrent infection and ulceration	13
23	F	3	Labium majus, clitoris	Recurrent infection and ulceration	9*
24	F	15	Labium majus, perineal region	Recurrent infection and ulceration	9*
25	F	1	Anogenital	Recurrent infection and ulceration	1*
26	F	1	Liver, spleen and disseminated skin	Life-threatening conditions	9*
27	F	3	Liver and disseminated skin	Life-threatening conditions	5*

* Treatment is ongoing.

hypertension, gastric irritation, systemic infections, particularly fungal infections, changes in personality, metabolic side effects and cushingoid changes; neurodevelopmental impairment and failure to thrive in long term.^{5,10,11} Because of these side effects, use of CS have been restricted.

During infancy and childhood, propranolol has been safely used agent for nonhemangioma indications for many years. In 2008, Léauté-Labrèze et al. reported that they used propranolol in a infant for hemangioma caused heart failure and they detected regression of hemangioma with propranolol treatment.¹¹ So after this incidental invention, propranolol has been started to be used for treat-

ment of hemangiomas around the world. Recently, propranolol has taken the place of CS therapy and it has become the first-line therapy choice in hemangioma treatment.

Propranolol is a non selective β -blocker and have rare side effects including symptomatic hypoglycemia, bronchial hyperreactivity, hypotension, seizure, restless sleep, constipation, and cold extremities. In our study, there was no observed side effects of propranolol. However, in the literature the rate of side effects of propranolol were reported in a wide range 0.8-26.7%.^{5,16,17,19} These reported side effects of propranolol treatment were cool extremities (26.7%), irritability (17.1%), lower



FIGURE 2a-e: (Patient number 12) An infant with periauricular hemangioma received propranolol because of cosmetic indication. (a) at 4 months of age (b) at 6 months of age (c) at 12 months of age (d) at 15 months of age (e) at 24 months of age.



FIGURE 3a-d: (Patient number 4) An infant with hemangioma localized in upper lip received propranolol. (a) at birth (b) at 3 months of age (c) at 6 months of age (d) at 16 months of age.

gastrointestinal upset (14.3%), poor feeding (7.6%), lethargy (4.8%), rash (0.8%), emesis (12%), hypotension (10.5%), broncospasm (0.8%), bronchial hyperreactivity (21%), bradycardia (8%) in different studies.^{16,17,19} Propranolol is a relatively safe drug that has been used during infancy and childhood for many years. In recent years experiences of hemangioma treatment with propranolol have been accumulated, consequently nowadays usage of propranolol is generally acknowledged for the first-line treatment of hemangioma by clinicians and parents. Also, treatment of some complicated visceral hemangiomas with propranolol have been reported.^{12,13,20-22} Suggested therapeutic mechanism of propranolol was inhibition of angiogenesis and induction of apoptosis in endothelial cells.²³

Propranolol has been used for hemangiomas in our clinic since 2009. Herein we presented the treatment experience with oral propranolol in 27 patients with hemangioma. In our study, pallor and partially regression in all patients have achieved 4-6 weeks. Also, previous studies have reported rapidly partially regression and transformation of color in hemangiomas.^{16,17,19} All patients who completed propranolol treatment have showed complete involution with minimal residue and also no recurrence at cessation of the therapy. By different studies in the literature involution rates of treatment ranging from 80 to 100% was given and they reported no recurrence.^{16,17,19,24} Syrup form of propranolol is not available in Turkey. The propranolol solution was prepared by using 40 mg tablet form of drug, but dissolution of drug in water was difficult. We had some difficulties to adjust the current dosage of drug in our 14 patients (52% of all

because their body weight was <3000 g. Despite these difficulties we educated the parents about preparation and usage of propranolol and also possible side effects. In this way, we did not hospitalized any of our patients for propranolol treatment. None of the patients in our study experienced significant symptomatic side effects from propranolol use.

Especially for hemangiomas occurring in the head and neck area, due to the first-year steadily growing characteristic of lesions, concerns of families may leave clinicians in difficult situations. From the knowledgeable families, propranolol treatment option is among the most frequently asked questions. Even if no treatment indication, these patients are known that they had applied to many centers. Among our patients there are cases which we have started their treatment due to this reason. Its easier applicability in an outpatient setting together with its safety show that propranolol can also be used easily with polyclinic controls in this patient group.

CONCLUSION

Propranolol is a well-tolerated, efficacious, and safe drug for treatment of infantile hemangiomas. Propranolol can be initiated and administered in the outpatient setting for patients with hemangioma. Despite some difficulties about adjusting the current dosage of propranolol, tablet form of drug can be used for treatment by preparing solution for low weight infants. Treatment indications may become more flexible taking into account of the safety profile of propranolol.

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