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RESEARCH

Cardiac screening in patients with infantile hemangiomas before propranolol treatment

İnfantil hemanjiom tanılı hastalarda propranonol tedavisi öncesi kardiyak değerlendirme

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Abstract

Purpose: The aim of this study is to evaluate the cardiac findings of patients with Infantile hemangiomas (IH) prior to propronalol treatment and to compare our findings with literature data and verify the need for detailed cardiac screening.

Materials and Methods: We performed a single-center retrospective review of patients diagnosed with IH who underwent cardiac screening between October 2021 and October 2022. Charts were reviewed and symptoms, heart rate, blood pressure, electrocardiogram, and echocardiogram findings were recorded for each patient.

Results: Of the 50 patients, 30 were female. The mean age and weight were 7.1±7.3 months and 7.6±3.0 kg. Electrocardiography screening did not reveal any contraindication for treatment. Propranolol significantly reduced heart rate and systolic blood pressure (baseline: 120.2±10.5 bpm/89.6±17.6 mmHg; 1st week: 118.5±10.4 bpm/88.7±17.5 mmHg; 2nd week: 117.8±9.5 bpm/88.7±17.3 mmHg; 2nd month: 116.5±9.4 bpm/88.6±17.3 mmHg). Diastolic pressure reduction was significant only between 'baseline- 1st week and 'baseline- 2nd month (58.9±15.6 vs 58.2±15.8 mmHg; 58.9±15.6 vs 57.9±15.5 mmHg, respectively).

Conclusion: Screening electrocardiography and hospitalization for initiation of propranolol therapy is not necessary in most infants. Given the low frequency of complications, it seems medical history and physical examination are the cornerstones for safe initiation and monitoring of β-blocker treatment. Electrocardiography and BP control should be part of the pretreatment evaluation in high-risk patients.

Keywords: Infantile hemangioma, propranolol, electrocardiogram

Öz

Amaç: Çalışmamızın amacı, infantile hemanjiom tanılı hastaların propronalol tedavisi öncesi kardiyak bulgularını değerlendirmek, bulgularımızı literatür verileriyle karşılaştırarak ayrıntılı kardiyak taramanın gerekliliğini tartışmaktır.

Gereç ve Yöntem: Ekim 2021- Ekim 2022 tarihleri arasında, tek merkezde infantil hemanjiom tanısıyla propranolol tedavisi başlanan hastalar retrospektif olarak değerlendirildi. Tedavi öncesinde yapılan elektrokardiyografi ve ekokardiyografi sonuçlarının yanı sıra hastaların propranolol doz şeması, tedavi sırasında görülen semptomları, kalp hızı ve kan basıncını içeren fizik muayene bulguları geriye dönük olarak incelendi.

Bulgular: Toplam 50 hastanın 30'u kadındı. Hastaların yaş ortalamaları 7,1±7,3 ay, kilo ortalamaları ise 7,6±3,0 kg idi. Elektrokardiyografik (EKG) değerlendirmede tedavi başlanmasına engel bir durum saptanmadı. Propranolol tedavisinin, kalp hızı ve sistolik kan basıncını istatistiksel anlamlı ölçüde azalttığı izlendi (başlangıç: 120,2±10,5 dk/89,6±17,6 mmHg; 1. hafta: 118,5±10,4 dk/88,7±17,5 mmHg; 2. hafta: 117,8±9,5 dk/88,7±17,3 mmHg; 2. ay: 116,5±9,4 dk/88,6±17,3 mmHg). Diyastolik kan basıncının ise 'başlangıç-1. hafta' ile 'başlangıç- 2. ay' karşılaştırmasında anlamlı olarak azaldığı izlendi (sırasıyla 58,9±15,6 ve 58,2±15,8 mmHg; 58,9±15,6 ve 57,9±15,5 mmHg).

Sonuç: Propranolol tedavisi öncesi EKG ve hastane yatışının her hastada gerekli olmadığı yönündedir. Düşük yan etki profili göz önüne alındığında kılavuzların önerisi doğrultusunda hasta bazlı, öykü ve fizik muayenenin ön planda tutulduğu değerlendirme önerilmekte; elektrokardiyografi ve kan basıncı takibinin gerekliliği riskli hasta grubu için akılda tutulmalıdır.

Anahtar kelimeler: İnfantil hemanjiom, propranolol, EKG

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INTRODUCTION

Infantile hemangiomas (IH) are frequent, benign, classified as glucose transporter-one (GLUT-1) positive vascular tumors in infancy that affect almost 10% of children[1,2]. Majority of hemangiomas in infancy resolve spontaneously and only a small proportion of the cases with IHs requires treatment. The location of the lesions, size or associated morbidity like bleeding, visual obstruction, cardiac failure, airway compression, ulceration, and risk of the persistent residue of the hemangioma necessitates systemic medical treatment[3,4]. Since antiproliferative effect of propranolol was first described in 2008, it has become the first-line treatment because of its safety and high success rate (98%)[5-8]. The mechanisms of action of propranolol treatment are suggested to be pericyte-mediated vasoconstriction, inhibition of the neovascularization and cathecolamine-induced angiogenesis, induction of apoptosis in endothelial cells and inhibition of renin-angiotensin system[9]. Although there are several studies demonstrating the safety and effectiveness of propranolol treatment, physicians and families still continue to have concerns regarding cardiovascular effects of medication. Therefore, many centers still routinely hospitalize these patients to monitor possible symptoms and cardiovascular adverse effects. Although electrocardiogram (ECG) and echocardiogram (ECHO) screening before treatment has been advocated due to some of its potential side effects, the extent and need for pre-treatment cardiac evaluation are currently being discussed since its utility remains unclear[10,11]. Therefore, the aim of our study is to document our results to contribute the literature about the impact and necessity of cardiac assessment before propranolol therapy.

MATERIALS AND METHODS

Study design

We performed a retrospective review of all patients diagnosed with IH at Antalya Research and Education Hospital between October 2021 and October 2022. All fifty-three patients who were evaluated by the same Pediatric Hematologist for the indications of oral propranolol treatment and referred to pediatric cardiology clinic were evaluated. Therefore, there was no need to carry out the power analysis. Epidemiological, demographic, and clinical data were collected from clinical charts. Pre-treatment cardiac assessment data for each patient included medical history, extensive family history (connective tissue disease, autoimmune disease, congenital cardiac defects, or sudden cardiac death), physical examination, electrocardiogram and echocardiogram results were reviewed from medical records. Propranolol dosing protocol, patient experiences, and symptoms including bradycardia, diarrhea, seizures, cold extremities, allergic reactions, wheezing and sleep disturbances were also collected via outpatient visit notes[12]. Patients were divided into 4 groups (0–3 months, 3–6 months, 6–12 months, >12months) to compare the "baseline" and mean "1st week" measurements.

The exclusion criteria for treatment were the presence of prior known structural heart defects, congestive heart failure, arrhythmia, and obstructive pulmonary disease. Three patients were excluded from the study because of hemodynamically important ventricular septal defect. Complications such as ulceration, compression of a vital structure such as the eye and airway, proximity to an orifice, complications such as ulceration and large hemangiomas were the indications for systemic medication[11].

This study was approved by the Institutional Ethics Review Board of Antalya Research and Education Hospital (No: 1/13; 12/01/2023).

Cardiac screening

Electrocardiographic and echocardiographic examinations were performed by same pediatric cardiologist blinded to clinical outcomes (OT). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were described with the criteria of systolic hypotension <5 percentile oscillometric/2 SD of normal auscultation as follows; newborn: <57 mm Hg /64 mm Hg, 6 months: <85 mm Hg /65 mm Hg, 1 year: <88 mm Hg /66 mm Hg[11]. Pre-treatment ECG was obtained based on our clinical protocol. The same specialist interpreted all 12-lead ECGs including baseline parameters to detect bradycardia and/or any cardiac conduction disturbances. Bradycardia was defined as a heart rate (HR) below normal for age and gender[11]. Philips Affiniti 50 Cardiac Ultrasound; Bothell, WA, United States of America; 8-1 MHz transducer was used for echocardiographic evaluation. Two-dimensional (2D), M-mode, continuous-wave, pulsed wave, and tissue Doppler echocardiographic images were

obtained. Echocardiographic findings such as false tendon in the left ventricle, patent foramen ovale, and left superior vena cava were considered normal and were not reported as abnormalities. None of the patients received sedation before cardiac screening.

Propranolol regimen and follow-up

In patients with normal cardiac evaluation propranolol was started as an outpatient in accordance with the current guidelines unless the patient had safety concerns requiring inpatient observation (increased risk of side effects, pain or age <1 month). None of the patients received any treatment prior to β-blocker therapy. The starting dose of propranolol was 1 mg/kg/day in 2 doses. Families were informed explicitly about administration of the medication, signs and symptoms of side effects. One week later (1st week), all patients were clinically evaluated with physical examination, HR, BP and asked to report any adverse events. The dose was increased to 2 mg/kg/day and adjusted for weight. After the second evaluation, patients were re-evaluated in 2nd week and 2nd month. ECG was obtained in 2nd month of the treatment. None of the patients received any treatment for hemangiomas prior to β-blocker therapy.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 26.0. Quantitative variables were reported as means, medians, standard deviations and ranges. All data were checked for normality using the Skewness–Kurtosis test combined with a visual inspection of the histograms and the Q–Q plots. Data were also checked for homogeneity of variance using Levene's test. Since the conducted tests indicated that all the variables used in the study follow a normal distribution, parametric tests, specifically the paired t-test between baseline and 1st week group, baseline and 2nd week group and baseline and 2nd month groups of HR and BP variables, and Analysis of variance for repeated measures for the same variables measured repeatedly at four time points, were employed. A P-value <0.05 was accepted as significant.

RESULTS

A total of 50 patients (30 female, 60 %) were included in the study. At presentation, the mean age and weight were 7.1±7.3 months and 7.6±3.0 kg, respectively. Four patients, <1 month of age; were admitted to hospital and monitored for possible side effects (2-4 days). A large majority of patients had hemangiomas on the head (n=16, 32%) or neck (n=10, 20%), and 3 (6%) patients had IH in more than one location. During first week of treatment, 3 patients (6%) had diarrhea and 3 (%6) patients experienced sleep disturbances with excessive crying. These symptoms lasted for a few days and none necessitated hospitalization or discontinuation of treatment. No major side effects were observed throughout the course of treatment. All demographic and clinical characteristics of patients are listed in Table 1.

Table 1. Demographic and clinical characteristics of patients

Characteristics	n=50 (%)
Age at start of treatment	
Mean age ± SD	7.1±7.3
Age<1 mo	4 (8%)
Sex (female, %)	30 (60%)
Weight (kg)	7.6±3.0
Cardiac family history (n, %)	0 (0%)
Localization of hemangioma	
Head	16 (32%)
Neck	10 (20%)
Buttock	6 (12%)
Genitalia	5 (10%)
Trunk	5 (10%)
Extremities	5 (10%)
More than one location	3 (6%)

Mean age ± SD; mean age± standard deviation, mo; month old (n,%)

None of the patients' age-adjusted baseline HR revealed evidence of bradycardia. When baseline and during treatment (1st week, 2nd week and 2nd month) values were compared, all patients had a statistically significant reduction in HR ($p<0.01$). Moreover, patients were divided into 4 groups (0–3 months, 3–6 months, 6–12 months, >12months) to compare the "baseline" and mean "1st week" measurements. HR was significantly decreased in all patients ($p<0.01$); patients aged 0–3 months had a mean reduction of 14.8 beats/min, aged 3–6 months had 13.3 beats/min reduction, however patients aged >6 months had milder reductions.

There was a significant decrease in SBP between all groups ($p <0.01$). However, similarly to HR data, patients aged 0–3 months and 3–6 months had a statistically significant SBP reduction of 5.1 mmHg

and 3.1 mmHg, respectively ($p < 0.05$), patients aged >6 months had milder reductions. DBP reduction was significant between 'baseline-1st week' and 'baseline–2nd month' ($p<0.02$ and $p=0.01$, respectively), DBP showed no significant difference between the other groups ($p>0.05$). Changes in vital signs were summarized in Table 2.

Table 2. Heart rate and blood pressure at baseline and propranolol initiation period

	Baseline	1st week	2nd week	2nd month	p1	p2	p3
HR, beats/minute	120.2±10.5	118.5±10.4	117.8±9.5	116.5±9.4	<0.01	<0.01	<0.01
SBP, mm Hg	89.6±17.6	88.7±17.5	88.7±173	88.6±17.3	<0.02	<0.03	<0.01
DBP, mm Hg	589±15.6	58.2±15.8	58.1±15.8	57.9±15.5	<0.02	0.05	0.01

Note: Data are given as mean ± SD, mean ±standard deviation, DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure. p1: Baseline vs.1st week groups, p2: Baseline vs.2nd week groups, p3: Baseline vs.2nd month groups, * $p<0.05$-values were considered statistically significant.

All patients underwent ECG and ECHO evaluation, as it was the inclusion criteria of the study. Three patients were excluded from the study because of hemodynamically important ventricular septal defect. ECG screening did not demonstrate any contraindications for medication across the cohort. Seven (14%) patients showed minor ECG abnormalities; ectopic atrial rhythm (n=1, 14.2%), right bundle branch block (n=1, 14.2%), atrial ectopic beats (n=2, 28.4%), ventricular ectopic beats (n=1, 142%), and QTc prolongation (n =2, 28.4%). Both of the patients with QTc prolongation (465 and 472 ms) were diagnosed as drug-induced long QT, control ECGs were normal after drug discontinuation (clarithromycin).

Echocardiographic evaluation was abnormal in 11 (22%) patients; 6 (54.6%) with secundum atrial septal defect, 2 (18.1%) with small ventricular septal defect, and 3 (27.2%) with patent ductus arteriosus.

DISCUSSION

Although the majority of IH lesions spontaneously regress without treatment, 10-15% of the lesions are significantly complicated and require referral to Pediatric Hematologist for treatment evaluation[4,13]. In the recent years, oral propranolol has been considered as the first-line treatment with a low adverse effect profile and high effectiveness[2,4-7]. In spite of the common use of ECG and ECHO in screening of IH patients before the use of propranolol, its' efficacy remains uncertain. The aim of this study is to evaluate the cardiac findings of patients with IH prior to propronalol treatment and to compare our findings with literature data and verify the need for detailed cardiac screening. No contraindication was detected in any patient by ECG screening and no major adverse event was documented during the short-term follow-up. Therefore, our data support previously published studies, providing further confirmation that pre-treatment ECG is not necessary for most patients with IH and limited cardiac screening approach recommended in the consensus guidelines is a reliable approach[3,14,15].

Cardiac screening before propranolol treatment has shown no pathological data in multiple studies, but still, several outcomes are drawn[16,17,18]. Consensus guidelines published in 2013, for propranolol treatment of IH included a recommendation for ECG testing for patients in high-risk groups: bradycardia for age (newborns-1 mo <70, 1–12 mo <80, children <70 beats/minute), presence of an arrhythmia, family history of congenital heart disease or arrhythmia· Major contraindications of β-blocker therapy in hemangiomas is PHACE syndrome and congestive heart failure. However, heart failure is a clinical diagnosis, a detailed history and a physical examination is enough to detect these patients[11]. Therefore, they did not suggest cardiac evaluation routinely before initiation of treatment[10,11,17,19-22]. In contrast, Blei et al. and Dyme et al. suggested cardiac evaluation, as the number of IH cases being treated with propranolol are increasing; contraindications for propranolol may also presumably increase[16,17]. In light of all these studies, since contraindications for propranolol are infrequent a consensus report suggested an indication related cardiac screening approach[11]. Most recently, a large scale multicenter study evaluating 783 patients was published supporting limited monitoring in the setting of thoroughgoing prescreening[23].

In our study, we also focused on the effects of

propranolol on cardiovascular parameters like HR, systolic and diastolic BP. We reported that there were statistically significant reductions in HR and SBP measurements but there was no significant decrease in the mean of DBP. Although, blood pressure Z scores and percentiles normalized by age, sex, and height describe hypotension in children, it is difficult to provide age-based parameters to define systolic hypotension in infants. So, some of the guidelines tried to describe systolic hypotension <5 percentile oscillometric/ 2 SD of normal auscultation as follows; 0-1 mo: <57 mm Hg /64 mm Hg, 1- 6 mo: <85 mm Hg /65 mm Hg, 6 mo-1 year: <88 mm Hg /66 mm Hg. Patients who have SBP measurements below these values during propranolol initiation or dose adjustment ensure careful consideration for additional evidence of cardiovascular risk and continuation of propranolol should be considered at higher risk. Although, consensus guidelines and renewed FDA prescribing information recommend monitoring HR and BP 1-2 hours after initiation of propranolol and each dose increase, many centers create alternative follow-up protocols according to clinic routines[11,24,25]. A survey by Kumar et al. showed that only 25 percent of physicians carry out the following suggested guidelines exactly[26].

During our study, no patients experienced symptomatic hemodynamic changes after dose initiation or dose augmentation despite significant HR and SBP reduction and there were no major cardiac adverse events reported by parents. Similar to our findings Bar et al. also reported decrease in BP and HR. They did not report any symptomatic major side effects including hypoglycemia, bradycardia or hypotension while few non-symptomatic adverse events, not necessitating treatment discontinuation or dose decrease were recorded, including hypoglycemia and asymptomatic bradycardia or hypotension, depending on the chosen reference criteria. Although these adverse effects were asymptomatic they recommended ambulatory short term monitoring for patients at high risk of developing hypoglycemia and hypotension: preterm and very low weight infants, those with a history of hypoglycemia, and younger patients (<6months) since they have a higher reduction in both systolic BP and HR compared to older ones[27]. Unlike our data, Xu et al. reported no significant decrease in SBP and mean HR[11,28]. Unfortunately, in our study, patients were not monitored 1-2 hours after the initiation of treatment as recommended in the guidelines. This may have caused us to miss some early symptoms and findings during the study.

Experience with propranolol therapy has significantly increased in the past decade and reported side effects of propranolol are mild and transient, however most of the healthcare providers still have some concerns about starting treatment as an outpatient[29,30]. In a retrospective study examining 2290 patients admitted to the hospital for treatment with propranolol for IHs very few patients were found to suffer from treatment-related side effects which, potentially results in unnecessary admission and increased cost of care. Patients with neurological or neuromuscular conditions and those with respiratory conditions appear to be at greatest risk of both prolonged hospitalization and readmission[31]. At this point education of families for possible side effects is important in the success of the drug therapy. This information should be given to the families at the first visit.

Our study presents the experience of a single tertiary Pediatric Hematology and Cardiology center. The study's retrospective nature, small patient cohort, and relatively short follow-up duration are its main limitations. Although we did not obtain any history of major side effects from families after propranolol administration, asymptomatic side effects like hypotension and hypoglycemia can be missed especially in small infants. In addition, it is difficult to distinguish whether the symptoms experienced in infants are directly related to the side effects of propranolol or unrelated etiologies. One of the side effects of propranolol is hyperkalemia, and it can have an impact on cardiac evaluation. It was one of the limitations of the study that the blood biochemistry (especially in terms of K) was not checked during the evaluation of the patients.

In conclusion, our data support previously published studies, providing further approval that screening ECG and hospitalization for initiation of propranolol therapy is not necessary in the majority of infants. The best approach for screening is not clear but given the low frequency of complications, it seems personalized, limited screening is appropriate as proposed in the consensus guidelines. A thorough medical history and physical examination is the cornerstone for safe initiation and monitoring of β-blocker treatment. ECG monitoring can be reserved for patients potentially at risk such as, patients with a cardiac family history including arrhythmia, congenital heart disease, sudden cardiac arrest, or

connective tissue disease. For high-risk patients like preterm infants and younger patients (<6 months) ambulatory short-term monitoring for glucose levels and BP control should be kept in mind. Although there are several data in the literature, future studies with larger cohorts are needed for additional guidance in determining the safest and most cost-effective protocols.

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