

Cardiac evaluation in children with hemangiomas

Hemanjiyomu olan çocuklarda kardiyolojik değerlendirme

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ABSTRACT

Objective: Hemangiomas are tumors most commonly encountered in pediatric patients, and are frequently treated with propranolol. However, there are currently no standard methods for evaluating cardiac function in patients prior to propranolol treatment. The present study was designed to aid in the evaluation of pretreatment cardiac and effects of propranolol on vital signs in pediatric hemangioma patients.

Methods: A pediatric oncology specialist and a pediatric cardiology specialist examined all patients prior to initiation of propranolol treatment. All patients were examined by the same 2 physicians. Cardiac evaluation included complete echocardiogram and electrocardiography. From September 2009 to January 2014, 146 patients aged 4 days to 10 years were screened.

Results: No patient had cardiac contraindication to propranolol. The effect of hemangioma on left ventricle size was examined, but left ventricle dilatation was found in only 3 patients. However, 68 patients had abnormal echocardiogram: 17 had patent foramen ovale, 4 had ventricular septal defect, 9 had atrial septal defect (associated with right heart enlargement), 8 had patent ductus arteriosus, 6 had physiologic pulmonary stenosis, and 1 had an aortic coarctation. No contraindications to propranolol or side effects were observed. However, cardiac anatomic defects were more common in this patient group than in the general population.

Conclusion: Hemangiomas in infants or children, even in small or premature infants, can be treated with propranolol without significant cardiac side effects. In addition, large dermal hemangiomas were not found to affect ventricular size in pediatric patients.

Infantile hemangiomas are histologically benign vascular lesions frequently encountered in infants.^[1,2] While they are benign, medical treatment is often necessary due to size or associated morbidity.

ÖZET

Amaç: Hemanjiyomlar küçük çocuklarda en sık görülen tümörlerdir ve gerekli olduğunda propranolol ile tedavi edilirler. Propranolol tedavisi başlanmadan önce kardiyolojik değerlendirme için standart yöntemler henüz bulunmamaktadır. Bu çalışma pediatrik hemanjiyom hastalarında tedavi öncesi kardiyak durumun ve propranololün yaşamsal bulgulara etkilerini değerlendirmeye yardımcı olmak için tasarlandı.

Yöntemler: Bütün hastalar propranolol tedavisine başlamadan önce aynı pediatrik kardiyolog uzmanı ve onkolog uzmanı tarafından değerlendirildi. Kardiyak değerlendirmede ekokardiyografi ve elektrokardiyografi kullanıldı. Eylül 2009 ve Ocak 2014 arasında yaşları dört gün ile on ay arasında olan toplam 146 hasta çalışmaya alındı.

Bulgular: Hastaların hiçbirinde propranolol kullanımı için kontrendikasyon yoktu. Ancak bu hastalarda anatomik defektler genel popülasyona göre daha sıklı. Hemanjiyomların sol ventrikül boyutları üzerine etkisi araştırıldı ve sadece üç hastada sol ventrikül genişlemesi saptandı. Ancak hastaların 68'inde ekokardiyografi ile bir patoloji saptandı. Bu patolojiler hastaların 17'sinde patent foramen ovale, 4'ünde ventriküler septal defekt, 9'unda atriyal septal defekt (sağ kalp boşluklarında genişlemeye sebep olan) 8'inde patent duktus arteriyozus, 6'sında fizyolojik pulmoner darlık ve 1 hastada aort koarktasyonu idi.

Sonuç: Hemanjiyomlar çocuklarda hatta prematüre bebeklerde dahi propranolol ile kardiyolojik yan etkiler görülmeden güvenle tedavi edilebilirler. Ayrıca, büyük cilt hemanjiyomları çocuk hastalarda ventrikül çapını genişletmemektedir.

Several systemic medications are used to treat hemangiomas, and propranolol was found to be an effective treatment in 2008.^[3,4] Since this discovery, propranolol has been advocated as the preferred

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treatment for hemangioma in infants in several studies.^[1,2,5–7]

Propranolol is a nonselective beta-blocker used to treat arrhythmias, hypertrophic cardiomyopathies, hypoxic spell prophylaxis, and hyperthyroidism in children. Bradycardia, hypotension, and myocardial depression are the main cardiac side effects of propranolol, and are usually dose-related. Hypoglycemia and bronchospasm can also occur as a result of propranolol treatment. Prior to treatment, the patient should be screened for medication-associated risks.

Pediatric hemangioma patients who received cardiac screening prior to study commencement that included physical examination, electrocardiography, and echocardiography, were retrospectively evaluated to determine cardiologic parameters and effects of propranolol on vital signs including heart rate and blood pressure.

METHODS

The present retrospective study was conducted between September 2009 and January 2014. All pediatric patients with hemangioma were administered 2–3 mg/kg/day of propranolol in 2 doses.

All patients were enrolled in accordance with the standards of the American Academy of Dermatology Guidelines/Outcomes Committee.^[8] Initial clinical evaluation was performed using photographs. Patients were referred to a pediatric cardiologist to rule out cardiovascular disease. Peripheral blood count, blood urea nitrogen, creatinine, aspartate aminotransferase, and alanine aminotransferase were measured to rule out systemic disease. Informed consent was obtained.

Cardiac screening included medical history, physical examination, electrocardiography, and echocardiography. Echocardiograms were performed using an Acuson Sequoia (Siemens AG, Berlin, Germany) or a Vivid i (GE Healthcare, Little Chalfont, UK). Full echocardiograms were performed in all patients, including 2-dimensional, M-mode, Doppler, and color Doppler examinations.

Propranolol was initiated in-hospital. Due to the absence of other preparations in Turkey, 40-mg Dideral tablets (propranolol hydrochloride; Sanofi-Aventis, İstanbul, Turkey) were used for treatment.

Tablets were dissolved in 20 mL of distilled water. The solution was stored in a refrigerator for 24 hours and shaken before each use. Initial,

oral, dose was 1 mg/kg/day for patients under 3000 g. If this dose was tolerated well, it was increased to 2 mg/kg/day. The drug was administered in 2 doses to all patients. Heart rate and blood pressure were monitored hourly during the first day of treatment. In the absence of side effects, treatment was continued at home, and the patient was reevaluated after 10 days, then every month. Telephone consultation was held with parents of patients whenever necessary, and any side effect was noted. Clinical examination was performed at every follow-up visit. Side effects were also noted while monitoring treatment compliance and tolerance. Body weight was measured for dose adjustment. Parents were informed about the interaction of other drugs with propranolol, particularly salbutamol therapy.

Clinical data of 146 pediatric patients who received propranolol are summarized in Table 1. Forty of the 106 patients were female (72.6%), and 29 (19.8%) were born preterm (<36 weeks). Median patient age was 4.8 months (4 days to 3 years), and 69.8% of patients were younger than 6 months.

Statistical methods

Data are presented as frequency with percentage, mean±SD, or median (minimum–maximum measurements). Pre- and post-treatment heart rate and blood pressure were compared using paired sample t-test.

RESULTS

Hemangiomas were located on the head and neck in 66 patients, and 15 patients had widespread hemangiomas. Mean hemoglobin level was 11.1±0.2 g/dL (minimum: 10.7–maximum: 11.5 g/dL) and was <12 g/dL in 62 patients (42.4%). Blood urea nitrogen, creatinine, aspartate aminotransferase, and alanine aminotransferase levels were within normal range for all patients. Heart murmurs were detected in 44 patients (30.1%), pathological murmurs in 14 and innocent murmurs in 30 patients.

Physical examination data, heart rate, and left ventricular end-diastolic diameter (LVEDD) dimension

Abbreviations:

ASD	Atrial septal defect
LVEDD	Left ventricular end-diastolic diameter
PDA	Patent ductus arteriosus
VSD	Ventricular septal defect

Table 1. Patient characteristics

Variable	Result
Number of patients	146
Sex (%)	
Male	27.4%
Female	72.6%
Age (months) median (minimum–maximum)	4.8 (4 days–3 years)
0–3 months	49 (33.5%)
3–6 months	53 (36.3%)
6–12 months	15 (10.2%)
>12 months	29 (28.7%)
Prematurity	29 (19.8%)
Weight (g) median (minimum–maximum)	3450±2900(2600–19000)
Birth weight (g) mean±SD (minimum–maximum)	2928±777 (570–4510)
Birth weight (<2500 g), n (%)	33 (22.6%)
Location of hemangioma, n (%)	
Head and neck	66 (45%)
Trunk	44 (30.1%)
Perineal	7 (4.79%)
Extremity	14 (9.58%)
Wide spread	15 (10.2%)
SD: Standard deviation.	

were examined prior to treatment, in order to assess the cardiovascular effects of hemangiomas. No clinical findings of heart failure were observed, with the exception of 2 children with large ventricular septal defects (VSDs).

All patients had normal sinus rhythm on electrocardiogram. Corrected QT was calculated in all patients (minimum: 0.35–maximum: 0.44), and no short- or long-QTs were observed. Heart rate, recorded by electrocardiogram, ranged from 85–173 beats/minute (128±17.6 beats/min) prior to initiation of propranolol treatment. Propranolol was initiated in the hospital, and heart rate and blood pressure were monitored. Mean heart rate over a 24-hour period was 129±10.9 beats/minute (minimum: 86–maximum: 154 beats/min). Final heart rate was 136±11.3 beats/minute (minimum: 98–maximum: 168 beats/min). No statistically significant difference in heart rate measured during the first 24 hours and final heart rate were found ($p<0.05$). Mean systolic blood pressure was 90±10 mmHg (minimum: 80–maximum: 110 mmHg) prior to propranolol treatment. Final systolic

blood pressure prior to discharge was 90±5 mmHg (minimum: 75–maximum: 100 mmHg). No statistically significant difference was found between first and final blood pressure measurement ($p<0.05$).

Thirty-nine patients had structural abnormalities (26.7%), 9 had VSD, 9 had atrial septal defect (ASD; associated with right heart enlargement), 8 had patent ductus arteriosus (PDA), 6 had mild pulmonary stenosis, 3 had first-degree mitral regurgitation, 2 had mild aortic regurgitation, one had mild aortic coarctation, and one had first-degree tricuspid regurgitation. Other echocardiogram results were patent foramen ovale in 17 patients (11.6%), minimal mitral regurgitation in 3 patients, mesocardia in 1 patient, and aneurysm of the interatrial septum 1 patient (Table 2). There was no relation between localization of hemangioma and type of cardiac defect.

Mean LVEDD was 21.5±0.3 mm (minimum: 20.9–maximum: 22.2). Z scores from LVEDD measurements were determined, and only 3 patients had LVEDD z score of >2.

Table 2. Cardiac and physical examination findings

		Result (Mean±SD or n)
Physical examination		
Heart rate (beat/min)	Pretreatment	128±17.6 (85–173)
	24 hours heart rates with propranolol	129±10.9 (86–154)
Echocardiographic/electrocardiographic findings		
Audible murmur	Innocent murmur	30
	Pathological murmur	14
	Total	44 (30.1%)
Structural abnormality	Ventricular septal defect	9
	Atrial septal defect	9
	Patent ductus arteriosus	8
	Pulmonary stenosis	6
	1 st degree mitral regurgitation	3
	Mild aortic regurgitation	2
	Mild aortic coarctation	1
	1 st degree tricuspid regurgitation	1
Total	39 (26.7%)	
Other cardiac abnormalities	Patent foramen ovale	17
	Minimal mitral regurgitation	3
	Mesocardia and aneurysm of interatrial septum	1
	Total	21 (14.38%)
Left ventricular dilatation		3
Cardiac intervention		5
Corrected QT		0.35–0.44
SD: Standard deviation.		

Cardiac intervention was anticipated in 5 patients: 2 with VSD, 2 with ASD, and 1 with PDA. Heart catheterization for aortic coarctation was recommended in 1 patient.

No cardiologic side effects such as bradycardia, hypotension, or arrhythmia related to propranolol were observed.

DISCUSSION

Routine echocardiography was presently performed in a large group of patients with hemangioma, as part of cardiac screening prior to initiation of propranolol therapy. No patient had cardiac contraindication, and incidence of contraindication, including arrhythmia, myocarditis, significant aortic stenosis, or aortic coarctation, is likely to be low in the general population.^[1,9–12]

A total of 26.7% of patients had structural cardiac abnormalities, a figure slightly higher than the percentage reported by Blei *et al.*,^[11] but significantly higher than other reported results (4–50/1000).^[11] These differences may be related to patient age; many younger infants were included in the present study, which may have increased the number of abnormalities detected, as the majority of cases of PDA, ASD, and small VSD close naturally over time. Cardiac intervention was anticipated in 5 patients: 2 with VSD, 2 with ASD, and 1 with PDA.

LVEDD was measured in all patients, and left ventricular dilatation was found in 3. Mean LVEDD was 21.5±0.3 mm (minimum: 20.9–maximum: 22.2). Z scores for LVEDD measurements were determined, and 3 patients had a score of >2. Of these patients, 2 had large VSDs. Hemangiomas are not thought to

affect left ventricle size. However, no data regarding this relationship was presently found.

Heart rate, blood pressure, and respiratory rate were monitored during treatment, and all were found to be within normal range. No significant difference ($p<0.05$) in heart rates measured following initiation of propranolol treatment was found. There have been no reports of death or serious morbidity related to propranolol, which is regularly used in infants and small children.^[12] Because propranolol is a β -adrenergic receptor blocker, several well-known side effects can occur, including bradycardia, hypotension, and bronchospasm. However, no cardiac side effects related to propranolol were presently observed. In a subsequent study, we plan to evaluate these children with 24-hour Holter monitorization in order to determine exact differences in heart rate.

Another important aspect of the present study was that 29 patients were preterm infants. In addition, 55 patients (37.6%) weighed less than 6 kg, and 6 patients weighed less than 3 kg. Use of propranolol in these patients demonstrates that it can be safely used in small infants without complication, similar to the results of our preliminary study.^[2]

Conclusions

Hemangiomas can be safely treated with propranolol in infants, even premature or small infants. Large dermal hemangiomas do not affect ventricular size. Although no significant contraindications or complications related to propranolol use were observed, cardiac screening and hospitalization of infants and children prior to treatment should still be performed.

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Ethical standards

The authors assert that all procedures contributing to this work comply with ethical standards of relevant national guidelines on human experimentation (Turkish Ministry of Health Good Clinical Practice Guidelines revised in 2014) and with the Helsinki Declaration of 1975, revised in 2008, and were approved by the relevant institutional committee (Institutional Ethics Committee for Human Studies).

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Anahtar sözcükler: Çocuk; hemanjiyom; kardiyovasküler parametreler; propranolol.