ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Relationship of Propranolol Treatment Success with the Location of Hemangioma and Patient Age: A Retrospective Study

Propranolol Tedavisi Başarısında Hemanjiyomun Yeri ve Hasta Yaşı ile İlişkisi: Retrospektif Çalışma

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ABSTRACT Objective: Propranolol causes shrinkage of hemangiomas through capillary vasoconstriction, increased endothelial cell apoptosis, and decreased vascular endothelial growth factors. This study aimed to evaluate the relationship between propranolol treatment success, the location of hemangioma and patient age. **Material and Methods**: Children with hemangiomas treated with propranolol between October 2016 and April 2019 were evaluated retrospectively. Propranolol was administered as 0.5 mg/kg/day. Vital signs, blood pressure and blood glucose were monitored while the dose was gradually increased to 2 mg/kg/day. Paling and shrinking of the lesions in monthly follow-ups were considered as success of the treatment. **Results**: The median treatment age in 31-children (61.3% females, 38.9% males) with hemangiomas was 6-month (1 months-16 years), the mean treatment duration was 7.74±3.66months (3 months-18 months). Hemangiomas located in head/neck-17 cases(54.8%), in trunk- 4 cases (12.9%), in genital/gluteal -4 cases(12.9%), in abdomen-4 cases (12.9%) and on extremities-3 cases (7%). Four (12.9%) patients had multiple hemangiomas. Three (9.7%) had hepatic hemangioma diagnosed prenatally. 51.6% of were between 1-3 cm^2. Blood glucose levels were stable in all. Propranolol therapy was ineffective in 4-patient aged 7, 8, 29, and 90-month, 3 with head and neck hemangiomas and 1 with trunk hemangioma. In 27-patient who had treatment success, propranolol was discontinued when the reduction in lesion size stabilized. **Conclusion**: Propranolol is preferred because of its ease of use, low side effects, cost-effectiveness, and rapid response. It can be successfully used even in liver hemangiomas by close monitoring of vital signs, blood sugar, and blood pressure. Treatment success of propranolol is independent of age and hemangioma location.

Keywords: Child; hemangioma; propranolol

ÖZET Amaç: Propranolol, kapiller vazokonstriksiyon yoluyla hemanjiyomların küçülmesine, artmış endotel hücre apoptozuna ve vasküler endotelyal büyüme faktörlerinin azalmasına neden olur. Bu çalışmada, propranolol tedavi başarısı ile hemanjiyomun yeri ve hasta yaşı arasındaki ilişkinin değerlendirilmesi amaçlandı. **Gereç ve Yöntemler:** Ekim 2016 ile Nisan 2019 tarihleri arasında propranolol ile tedavi edilen hemanjiyomlu çocuklar retrospektif olarak değerlendirildi. Üç günlük hospitalizasyonda vital bulgu, kan basıncı ve kan şekeri izlenirken, Propranolol 0,5mg/kg/gün'dan kademeli olarak 2 mg/kg/gün'e artırıldı. Aylık takiplerde lezyonların renginin solması ve küçülmesi tedavi başarısı olarak kabul edildi. **Bulgular**: 19'u (%61,3) kız, 12'si (%38,9) erkek olmak üzere hemanjiyomlu 31 çocukta medyan tedaviye başlama yaşı 6 ay (1 ay-16 yaş) idi. Ortalama propranolol tedavi süresi 7,74±3,66 ay (3ay-18ay)'dı. Hemanjiyomlar 17'sinde (%54,8) baş-boyun, 4'ünde (%12,9) gövde, 4'ünde (%12,9) genital/gluteal, 4'ünde (%12,9) abdomen, 3'ünde ekstremitelerde (%7) yerleşimliydi. Dört olguda (%12,9) birden fazla lokalizasyonda hemanjiyom mevcuttu. Prenatal tanılı üç olgu (%9,7) karaciğer hemanjiyomluydu. Hemanjiyomların çoğunluğu (%51,6) 1-3 cm^2 boyutundaydı. Tüm hastalarda kan glukoz seviyeleri stabildi. Yedi, 8, 29 ve 90 aylık 4 hastada propranolol tedavisi etkisiz kaldı, bunların 3'ünde baş ve boyun hemanjiyomu, 1'inde gövde hemanjiyomu vardı. Tedavinin başarılı olduğu 27 hastada propranolol tedavisi lezyon boyutundaki azalma stabilize olduğunda kesildi. **Sonuç:** Propranolol kullanım kolaylığı, düşük yan etkileri, uygun maliyeti ve hızlı yanıt vermesi nedeniyle tercih sebebidir. Propranolol, vital bulgu, kan şekeri ve kan basıncının yakından izlenmesiyle karaciğer hemanjiyomlarında bile başarıyla uygulanabilir. Propranololün tedavi başarısı yaş ve hemanjiyomun yerleşim yerinden bağımsızdır.

Anahtar Kelimeler: Çocuk; hemanjiyom; propranolol

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Congenital capillary hemangioma (infantile hemangioma, benign haemangioendothelioma, or strawberry nevus) is a benign vascular tumour that occurs at or within a few weeks after birth. Capillary skin hemangiomas, which are the most common primary benign tumours in infants, may be superficial, deep, or mixed (with both superficial and deep components).[1] Preliminary lesions are in the form of erythema, telangiectasia, and pale plaques and then take on their typical appearance. These early findings may be confused with pigment anomalies, vascular malformations, and traumatic ecchymoses.[2] Various complications such as bleeding, ulceration, infection, and compression findings can be seen in hemangiomas. Hemangiomas that develop complications and cause cosmetic concerns need to be treated.[3]

Propranolol therapy provides shrinkage of hemangiomas through capillary vasoconstriction, enhanced endothelial cell apoptosis, and reduced vascular endothelial growth factors. It is preferred in the treatment of hemangioma due to its ease of use, low side effects, cost-effectiveness, and rapid response.[3] In the present study, the results of propranolol therapy in hospitalized patients with hemangioma were evaluated.

MATERIAL AND METHODS

This retrospective study was approved by the Ethics Committee of Clinical Research of İstanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center (Decision number: 84, date of approval: 18.09.19) and conducted in accordance with the principles set forth in the Helsinki Declaration. Informed consents of all patients were obtained from their legal representatives.

Clinical findings, responses to propranolol treatment of hemangioma patients who were admitted to department of the pediatric surgery or consulted in the neonatal intensive care unit due to functional restrictions, those with bleeding hemangiomas, large lesions, those near the eye, on the lips in the genital regions even if they were under 3 cm in size, intra-abdominally located hemangiomas were evaluated from October 2016 through April 2019. The patients' photographs were taken before the propranolol therapy and their cardiovascular evaluation was performed by pediatric cardiologists via echocardiography. Platelet counts were assessed in all patients prior to the treatment. Transfontanelle and abdominal ultrasonography and color Doppler ultrasonography of the lesions were performed. To observe the side effects of propranolol, patients were hospitalized for the first three days of therapy.

For treatment, 40 mg tablet formula of propranolol hydrochloride (Dideral®, Sanofi Health Products Pharmaceutical Company, France) was used. One quarter of the tablet was dissolved in 10 mL of distilled water and mixed thoroughly before each use. The required doses were given on a full stomach. The initial dose of propranolol was determined as 0.5 mg/kg/day (divided into two doses), which was gradually increased to 2 mg/kg/day within 72 hours if no side effects, such as hypotension or hypoglycaemia, were observed.

Vital findings and blood pressure of the patients were measured every 2 hours and blood glucose level was measured every 8 hours. Patients who reached the maximum dose of propranolol with no side effects were discharged and asked to visit the outpatient clinic for the follow-up of treatment effects and possible side effects. Patients were controlled once a week for the first 2 weeks, then every two weeks, and then once a month. Legal representatives of the patients were informed about the side effects of propranolol therapy and advised to contact the hospital immediately in case of any problem. Physical examinations of the patients were performed at each visit and their photographs were taken for objective evaluations. Ultrasonographic examination was repeated when necessary (such as in cases with liver hemangioma, etc.). Body weights of the patients were also measured for dose adjustment and drug compliance and side effects were questioned.

Shrinkage in size, decrease in thickness and softening, change in colour from bright to pale red, and appearance of completely normal skin areas in the lesions were considered as regression of hemangioma. The treatment was discontinued if any side effects were observed in the monthly controls or in case of incompliance by the family. If there was no shrinkage

in the lesion at the 3rd month follow-up, treatment was considered unsuccessful, and the dose of propranolol was gradually decreased and discontinued.

STATISTICAL ANALYSIS

The data of the patients were analysed using the SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as numbers and percentages for categorical variables. Chi-square test was used to assess the relationship between hemangioma localization, age at which the treatment began and treatment success.

RESULTS

Children who were started on propranolol treatment for hemangioma in our pediatric surgery department and completed propranolol treatment for an average of six months within 2.5 years were included in this study. A total of 31 children [61.3% females (n=19), and 38.9% males, n=12] with hemangiomas aged between the age of 6 days and 16 years were evaluated. The admission age ranged between 1 days and 16 years, and 24 (77.4%) were under 1 year of age. Prenatal hepatic hemangioma was diagnosed in 3 (9.7%) cases. The median age of treatment initiation was 6 months (1 months-16 years); and the mean duration of the propranolol treatment was 7.74±3.66 months (minimum: 3 month-maximum: 18 months).

Hemangiomas were in the head and neck region in 17 cases (54.8%), in the trunk in 4 cases (12.9%), in the genital/gluteal region in 4 cases (12.9%), in the internal organs in 4 cases (12.9%) and on the extremities in 3 cases (7%). Four (12.9%) patients had hemangiomas in more than one place. Eight lesions (25.8%) were on the right, 13 (41.9%) were on the sagittal line and 10 (32.3%) were on the left side.

Sizes of the haemangioma lesions were <1 cm^2 in 3 cases (9.7%), >1-3 cm^2 in 16 cases (51.6%), >3-6 cm^2 in 9 cases (29%) and >6 cm^2 in 3 cases (9.7%). The area of the hemangioma was between 1-3 cm^2 in approximately half of the patients (51.6%).

Transfontanelle ultrasound findings were normal in 23 cases (74.2%) with open fontanelles. Echocardiographic findings were normal in 14 cases (45.2%), while 17 cases (54.8%) had abnormal findings. Patent foramen ovale was detected in 12 cases (38.4%); atrio-septal defect, mitral valve failure, patent ductus arteriosus, mild aortic valve failure and mild pulmonary stenosis were determined in one case each. Demographic properties and clinical findings of cases are summarized in Table 1.

One patient with a history of hypoglycemia in the neonatal period had mosaic Down syndrome, but no hypoglycemia was observed during his propranolol therapy initiated at the age of 13 months. The blood glucose levels were stable in all patients during their treatment. All patients had stable blood pressure on the first day of hospitalization; however, two patients developed hypotension on the 2nd and 3rd days of hospitalization, in which propranolol dose was reduced.

Propranolol treatments of patients were sufficient and effective in 27 (87.1%). As the decrease in hemangioma size stabilized in 27 patients, who responded to propranolol treatment for an average of 6 months, the propranolol dose was gradually reduced and then discontinued. Pre-treatment and post-treatment photography of some of the patients were seen in Figure 1, Figure 2, Figure 3, Figure 4 and Figure 5. Only one patient continued treatment until 18 months; pre-treatment and post-treatment photographs of this patient are seen in Figure 4A and 4B.

TABLE 1: Clinical findings of the cases with hemangioma.

Findings	n (%)
Sex	
Female	19 (63.1)
Male	12 (38.7)
Location of hemangioma	
Head and neck	17 (54.8)
Trunk	4 (12.9)
Genital-gluteal region	4 (12.9)
Internal organs	4 (12.9)
Extremities	3 (9.7)
Sizes of the hemangioma lesions	
<1 cm^2	3 (9.7)
1-<3 cm^2	16 (51.6)
3-<6 cm^2	9 (29)
≥6 cm^2	3 (9.7)

The lesions of 3 patients (9.6%) who started treatment when they were 2, 13 and 21 months of age regressed after an average of six months of propranolol treatment but increase in hemangioma sizes were observed at the 6th month follow-up visit. The lesion regressed in monthly follow-ups in the first case with a dose increase, and propranolol treatment was continued for 18 months. The other 2 cases whose lesions did not regress with an increase in dosage were sent to the plastic and reconstructive surgery department after the second six-month treatment. In all 3 cases, the lesions were in the head and neck region. Six-month propranolol treatment was unsuccessful in 4 cases (12.9%) who started propranolol treatment at 7, 8, 29 and 90 months of age. Three had hemangioma in the head and neck region and one had it on the trunk. A 29-month-old patient with hemangioma on his back was operated, and pathological examination was compatible with fibromuscular tissue. The other three patients were referred to plastic and reconstructive surgery. In terms of treatment success, no significant differences were found between the localizations of hemangioma (p=0.42) and the age at which propranolol treatment began (p=0.19). The success of propranolol treatment in hemangioma cases was summarized in Table 2.

DISCUSSION

Infantile hemangioma is a benign vascular neoplasm. The International Society for the Study of Vascular Anomalies (ISSVA) classifies infantile hemangioma lesions as vascular tumors that differ from vascular malformations.[4] Hemangioma is seen in 4% to 10% of infants and is predominant in girls.[5] Accordingly, in the present study, the ratio of female patients was higher. The occurrence of capillary hemangioma is more likely in siblings of an affected individual compared with the normal population.[1] However, none of our patients had a similar history in their siblings.

Although infantile hemangioma can develop in any part of the body, it is frequently seen in the head and neck region (33-60%).[6] In this study, the lesions were in the head and neck region in 54.8% of the patients. Hemangiomas of head and neck region adversely influence quality of life of patients as they

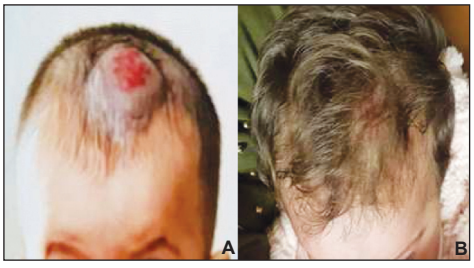

FIGURE 1: Before propranolol therapy (A) and after 6 months of propranolol therapy (B).

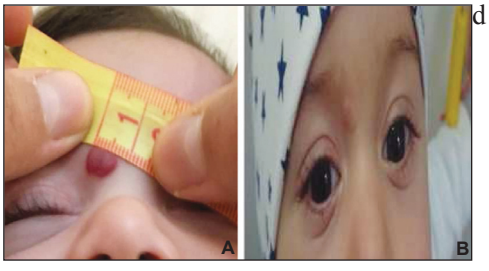

FIGURE 2: Before propranolol therapy (A) after 6 months of propranolol therapy (B).

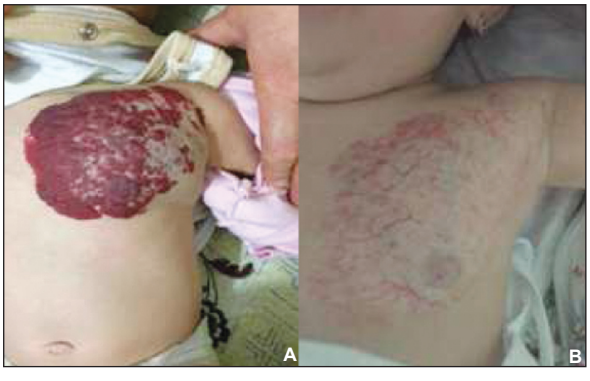

FIGURE 3: Before propranolol therapy (A) after 6 months of propranolol therapy (B).

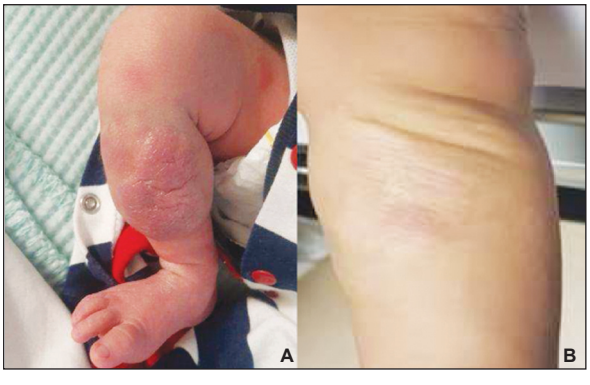

FIGURE 4: Before propranolol therapy (A) and after propranolol therapy (B); treatment was continued for 18 months.

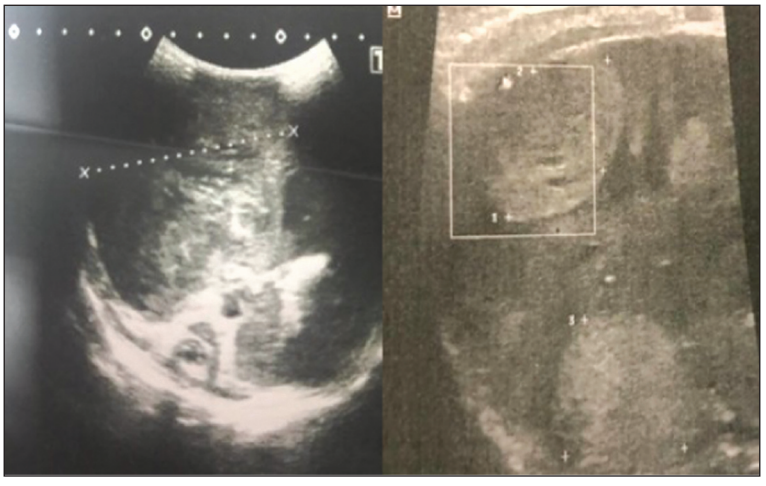

FIGURE 5: Before propranolol therapy (A): Size of hemangioma in liver was 90 mm and after propranolol therapy (B), size of hemangioma in liver reduced to 22 mm.

TABLE 2: The treatment success of the propranolol in cases with hemangioma.

	Successful treatment n (%)	Unsuccessful treatment n (%)	Success of the treatment (%)	p value
Location of hemangioma				
Head and neck	14 (45.2)	3 (9.7)	82	
Trunk	3 (9.7)	1 (3.2)	75	
Genital-gluteal region	4 (12.9)	0	100	
Internal organs	4 (12.9)	0	100	
Extremities	3 (9.7)	0	100	p=0.42
The age of starting treatment				
0-≤6 month	17 (54.8)	0	100	
6-≤12 month	5 (16.1)	2 (6.5)	71	
12-≤24 month	3 (9.6)	0	100	
>24 month	2 (6.5)	2 (6.5)	0	p=0.19

Chi-square Test; $p<0.05$ is significant.

rectly affect appearance. Hemangioma lesions in ear circumference, nose tip, lip circumference, and subglottic and tracheal regions can cause obstructions, while those in the periorbital region can lead to optic nerve compression, vision problems, and limited eyelid movements.[2] In addition, serious complications such as massive bleeding and infection can be observed in some types of lesions.

Hemangiomas have 3 phases in terms of biological behaviour.[4] In proliferating phase, endothelial cells proliferate, which causes clustered areas filled with large blood. Basic fibroblast growth factor and vascular endothelial growth factor are known to be responsible in this phase.[2] In involuting phase, fibrosis develops because of fibrous and adipose tissue accumulation around endothelial cell lobules and apoptosis occurs. The last phase is involuted phase, in which lesions grow progressively within 3-6 months and cause swelling on the surface. When a baby is 12-18 months old, lesions stop growing and become stable. After this phase, they will shrivel up and shrink in size.[1] Since 50%, 70%, and 90% of lesions regress at ages of 5, 7, and 9 years, respectively, most clinicians tend to approach with watchful waiting without immediate intervention.[6] This raises the question of whether the treatment started in the first 6 months of age in non-vital hemangiomas affects treatment success.

Although there is no need for radiological examination for typical skin hemangiomas, radiological examinations are helpful in differentiating hemangiomas from vascular malformations and other soft tissue tumors. Ultrasound and Doppler ultrasound provide differentiation of deep hemangiomas from other soft tissue masses.

Indications for hemangioma treatment include loss of function, complications (such as bleeding and/or infection), rapid growth, and a large lesion.[7] In the present study, propranolol therapy was started due to limb movement limitation in 1 patient, limitation of eyelid movement in 2 patients, and bleeding in 2 patients. Treatment was administered to prevent bleeding and infection due to diapering and dermatitis in genital hemangiomas and bleeding during teething in the lip hemangiomas. Apart from these, our indications of treatment also included large size lesions, which could potentially affect the child psychology, and intraabdominal lesions.

While most infantile hemangiomas do not leave any sequelae when regressed, they can sometimes remain in the form of atrophy, anetoderma, or fibrous-fatty mass. After an untreated tumor shrinks, the remaining skin degeneration, pigmentation, scars, or skin loosening affect the appearance and intervention may be required at the last stage.[6] Surgical correction may be required particularly for the coexistence of hemangiomas with lymphangioma.

According to the guidelines of ISSVA published in 2018, the treatment of infantile hemangiomas is mainly based on local and systemic drugs that inhibit vascular endothelial cell proliferation, promote tumor regression, and reduce tumoral residues.[8] Emergency treatment is suggested in hemangiomas with high and intermediate risks.[8] Previously, corticosteroids, interferon alpha, and chemotherapeutic drugs such as cyclophosphamide and vincristine were used in addition to local methods such as laser, intralesional steroid, and surgical removal in the treatment of infantile hemangiomas. Serious side effects such as Cushing's syndrome, growth retardation, hirsutism, arterial hypertension, cardiomyopathy, immunosuppression, and tendency to infection have been reported in the long-term use of oral steroids. Agents such as interferon-alpha, vincristine, and cyclophosphamide have also serious toxic side effects. Each of these approaches has its limitations in terms of therapeutic benefit and potential side effects.[7,9,10] On the other hand, Léauté-Labrèze et al. incidentally discovered and reported shrinkage in the periocular capillary skin hemangioma in the child with myocardiopathy during treatment with propranolol in 2008.[11] Henceforward, many local and systemic research have been conducted on this subject in the following years. Today, primary care in the treatment of infantile hemangiomas is propranolol, a non-selective β-adrenergic receptor blocker.[6] Inhibition of tumor cells, control of endothelial proliferation, and vasoconstriction are accepted as the therapeutic mechanisms involved in the treatment of infantile hemangiomas.[6] Propranolol is an effective and safe drug in shrinkage of hemangiomas.[6]

Several initial doses of propranolol have been reported for the treatment infantile hemangiomas.[4] The American Consensus Conference has suggested the initial dose of propranolol as 1 mg/kg/day and then a gradual increase to the dose of 2 mg/kg/day.[12,13] Other studies have also reported the use of 2-3 mg/kg/day and 0.75-1 mg/kg/day doses of propranolol.[14,15] Many studies have suggested to increase propranolol dose to 4 mg/kg/day for efficacy.[1] In the most recent data, no difference was reported between the propranolol doses of 2 mg/kg/day and 4.5 mg/kg/day in terms of therapeutic efficacy.[6] Therefore, the recommended dose of propranolol suitable for clinical use is 2-3 mg/kg/day.[6] In the present study, the initial dose of propranolol was determined as 0.5 mg/kg/day (divided into 2 doses), which was gradually increased to 2 mg/kg/day within 72 hours, if no side effects were observed.

Infantile hepatic hemangioma covers a spectrum of clinical conditions ranging from simple asymptomatic lesions to fatal complications. Respiratory problems and liver failure may be associated with common nodular type liver hemangiomas.[16] Propranolol has caused a marked change in infantile hepatic hemangioma treatment algorithm. Approximately one-third of patients with abdominal compartment syndrome require a liver transplantation in the period prior to propranolol therapy. This new treatment pre-

vents transplantation for many of these patients. Similar to the study by Sarıalioğlu et al., propranolol therapy was successfully applied even in liver hemangiomas in the present study.[16] Three of 27 patients who responded to the treatment had also hepatic hemangiomas and severe respiratory problems.

Vasoconstriction, bradycardia, hypotension, and hypoglycemia may be observed as side effects of propranolol therapy. Propranolol can cause a decrease in cardiac performance and early cardiac failure. For this reason, a complete cardiological examination with echocardiography should be performed before initiating the treatment. Vital signs and blood sugar level should also be closely monitored during treatment, every 8 hours.[10,17] In their study including 121 patients with infantile hemangioma, Lahrichi et al. reported side effects of propranolol therapy in 8% of the patients, bronchitis in 5 patients, hypoglycemia in 3 patients, and insomnia in 2 patients. In the present study, before starting propranolol therapy, all patients were evaluated with echocardiography by a pediatric cardiology specialist.[4] All patients had stable blood pressure on the first day of hospitalization; however, two patients developed hypotension on the 2nd and 3rd days of hospitalization and their propranolol doses were reduced. Similar to the study by Xu et al., blood sugar levels of our patients were also stable.[5]

In hemangioma patients unresponsive to treatment, radiological evaluations should be repeated. In the study by Özcan et al., 2 of the 5 treatment unresponsive patients were diagnosed with lymphangioma in their second radiological examinations.[18] In the present study, the pathological examination of the 29-month-old patient who did not respond to treatment and underwent surgery was consistent with fibromuscular tissue. In this patient, the treatment was unsuccessful and there were doubts about the diagnosis. The other 3 patients were directed to plastic surgery, not waiting for involution, because of the risk of bleeding due to the localization of the hemangiomas, which were in the lip and mouth. Similar to our study, no significant relationship was found between the age of starting propranolol therapy and treatment response in the study by Özcan et al.[18] However, Wu et al. reported that therapeutic efficacy of propranolol significantly increased in infants younger than 5 months of age.[6] They showed that size, depth, and location of infantile hemangioma did not affect the therapeutic efficacy of propranolol.[6] In the present study, treatment success was independent of the hemangioma location.

Although some studies have recommended discontinuation of propranolol when regression of hemangioma lesions stop, it has also been reported that propranolol therapy should be continued for at least 6 months and that rebound growth may occur if the treatment is discontinued early.[1,19] In the study including 25 patients with infantile hemangiomas, Xu et al. reported no recurrence when the propranolol therapy was discontinued.[5] They attributed this result to the continuation of the treatment for at least 6 months and the lack of patients younger than 2 months of age.[5] In the present study, propranolol therapy was continued for at least 6 months in 3 patients (aged 2 months, 13 months, and 21 months), in which the lesions re-enlarged when the therapy was discontinued.

CONCLUSION

Propranolol treatment can be administered successfully, even in liver hemangiomas, with close monitoring of vital signs, blood glucose and blood pressure of patients. Although the number of cases in our study is not quite sufficient, we can assume that the treatment success is independent of age and the location of hemangioma. However, this result should be supported by studies with large series.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Olga Devrim Ayvaz;* ***Design:*** *Olga Devrim Ayvaz;* ***Control/Supervision:*** *Olga Devrim Ayvaz, Ayşenur Celayir;* ***Data Collection and/or Processing:*** *Olga Devrim Ayvaz, Tuğçe Orbay, Sırma Mine Tilev;* ***Analysis and/or Interpretation:*** *Olga Devrim Ayvaz, Cengiz Gül, Ayşenur Celayir;* ***Literature Review:*** *Olga Devrim Ayvaz, Cengiz Gül, Merve Tuğçe Orbay, Sırma Mine Tilev, Ayşenur Celayir;* ***Writing the Article:*** *Olga Devrim Ayvaz, Cengiz Gül, Merve Tuğçe Orbay, Sırma Mine Tilev, Ayşenur Celayir;* ***Critical Review:*** *Olga Devrim Ayvaz, Cengiz Gül, Ayşenur Celayir;* ***References and Fundings:*** *Olga Devrim Ayvaz;* ***Materials:*** *Olga Devrim Ayvaz.*

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