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RESEARCH ARTICLE

Clinical and Treatment Management of Infantile Hemangiomas

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ABSTRACT

Objective: The majority of infantile hemangiomas (IHs) require observational follow-up, but for patients requiring treatment, the last decade has revolutionized treatment with the discovery of propranolol. Therefore, in cases requiring treatment, it would be appropriate to refer the newborn to the pediatric hematology and oncology department as soon as IH is detected during the first examination. In this study, we aimed to explain the clinical features and treatment selection features in patients with IH.

Materials and Methods: A total of 25 female and 15 male IH cases who applied to our pediatric hematology and oncology outpatient clinic were included in our study. Before treatment, all patients were evaluated with routine complete blood count, biochemical analysis, abdominal ultrasonography (USG), and pediatric cardiology. The diagnosis dates, treatment start dates, birth dates, the diagnosis of the lesion, monthly measurements after the start of treatment, and the treatment started and doses were recorded in the follow-up forms of the patients.

Results: The average age of the patients at the start of treatment was 6.5 months (2 months–15 months). Twenty-four of the patients were under 6 months old. In the treatment of IH, these patients were started with an oral propranolol solution preparation at a dose of 1 milligram (mg)/kg/day. In tolerant patients, the dose was increased to 2 mg/kg/day after 3 days. All patients received propranolol treatment for at least 6 months. In patients who started treatment after diagnosis, at least 50% and at most >95% involution occurred in the IH dimensions. No patient had pathological findings in the hemogram and biochemistry tests performed every 2 months.

Conclusion: In terms of ease of use, safety profile, and frequency of side effects, the use of oral propranolol solution was evaluated as very effective and tolerable, especially in the 2–6 month patient group. Additionally, propranolol was found to be quite effective in IH patients who were older than 6 months and whose treatment had not been started for different reasons. To confirm the diagnosis, the diagnosis should be clarified by USG/color Doppler USG, preferably by obtaining the opinion of a pediatric radiologist before starting treatment.

Keywords: Infant, hemangioma, propranolol, surgery, vascular malformation

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INTRODUCTION

Although systemic or intralesional corticosteroid first-line monotherapy was previously preferred in the treatment of infantile hemangiomas, due to side effects such as steroid-related hypertrophic cardiomyopathy, arterial abnormalities, heart disorders, eye disorders, external genital malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and high-output heart failure, it has lost its priority.[1]

Chemotherapeutic agents (vincristine, alpha-interferon), laser, surgery, or combinations of these treatments, which are among the other treatment options available for complicated hemangiomas, similarly provide limited therapeutic benefit due to their side effect profile and risks.[2–4] Therefore, propranolol, a non-selective beta-blocking agent, is used as first-line treatment in IHs due to its lower side effect profile and cost rates compared to other treatment options.[5]

The most commonly used first-line treatment for IH requiring systemic treatment is propranolol 1 mg/kg twice daily. Most infants can be safely started on propranolol as outpatients. Other treatment options reported in the treatment

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of complicated IHs include atenolol, nadolol, systemic corticosteroids, topical timolol, topical corticosteroids, topical imiquimod, intralesional corticosteroids, intralesional bleomycin, pulse dye laser, long pulse dye Nd:YAG laser, surgery, embolization, captopril, and sirolimus.[6]

MATERIALS and METHODS

Twenty-five female and 15 male infants who applied to our Pediatric Hematology and Oncology clinic were included in our study. Before treatment, all patients were evaluated with routine hemogram, biochemical analysis, abdominal USG, and pediatric cardiology. The patients' diagnosis dates, treatment start dates, birth dates, the diagnosis of the lesion, monthly measurements after the start of treatment, and the treatment started and doses were recorded in the patient follow-up forms.

Consent for publication was obtained from the patients' parents. Patients' parents gave informed written consent for their personal or clinical details, along with any identifying images, to be published in this study. Ethics approval and consent to participate were obtained from the institute hospital on 30.04.2024 with the ID no. 4385. This study complies with the Declaration of Helsinki and was performed according to ethics committee approval.

Statistical Analysis

Since this study included observational case information, only the demographic data of the patients were evaluated with the IBM SPSS 22 statistical power analysis method. Other findings were evaluated from patient records and study forms.

RESULTS

In our study group, the location of the IH was on the head in 21 (53%), on the trunk in 8 (20%), on the extremities in 5 (13%), on the pubis in 2 (6%), on the genitals in 2 (6%), and in more than 2 locations in 8 (20%) of the patients. The demographic and clinical characteristics of the patients are presented in Table 1.

One of the patients had a 332 centimeter (cm) sized hemangioma on the big toe of the left foot and the adjacent toe. When he was 3 weeks old, he had to be operated on by a plastic surgeon due to rapid growth, bleeding, and the risk of functional impairment. The pathology evaluation reported the mass as IH. It was observed that the disease did not recur in the big toe of the left foot during the 6-month follow-up of the patient.

Bleeding occurred in IHs in 4 of the patients. Acute bleeding in these patients was controlled by applying adrenaline gauze to the bleeding focus of the IH for 15 minutes to 2 hours. The patients continued their propranolol treatments.

Figure 1 displays the first month of starting treatment in a 10-month-old male patient who had a 452 cm sized IH in the presternal region, and Figure 2 displays the 6th-month images of propranolol treatment. It was observed that total involution was between 60–70% at the end of the 6th month. This patient's treatment still continues.

The average follow-up period of the patients was between 6 months and 12 months. The number of patients whose treatment continued for 6 months and who achieved involution above 90% was 28 (75%).

In Figures 3 and 4, images of a 3-month-old girl with IH of 344 cm size localized in the parieto-frontal region of the head are presented. Propranolol treatment was started with a dose of 2 mg/kg/day, and almost complete involution was detected at the end of the 6th month.

In Figures 5 and 6, propranolol treatment was started with a dose of 2 mg/kg/day for a 434 cm sized IH localized on the right leg of a 5-month-old male patient, and images of the patient with significant involution at the end of the 6th month are presented.

Table 1. Demographic and clinical characteristics of patients with Infantile Hemangioma

Variable	n	%
Gender		
Male	15	37.5
Female	25	62.5
Age		
1–6 months	24	60
6 months-2 years	16	40
Localization		
Head-neck	21	52.5
Body	8	20
Extremity	5	12.5
Genital	2	5
Pubis	2	5
Other	3	7.5
Treatment dose (Propranolol)		
2 mgr/kg/day	36	90
3 mgr/kg/day	4	10
Treatment response rate at 6 months		
<50%	0	0
50–90%	12	25
>90%	28	75

n: Number of patients; Mgr: Miligram

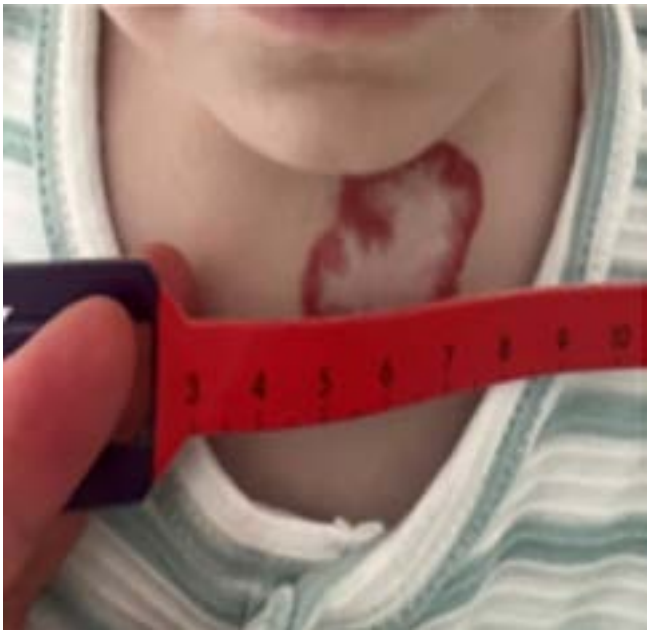

Figure 1. Image of a 4*5*2 cm infantile hemangioma in the presternal region of a 10-month-old male patient on the first day of treatment

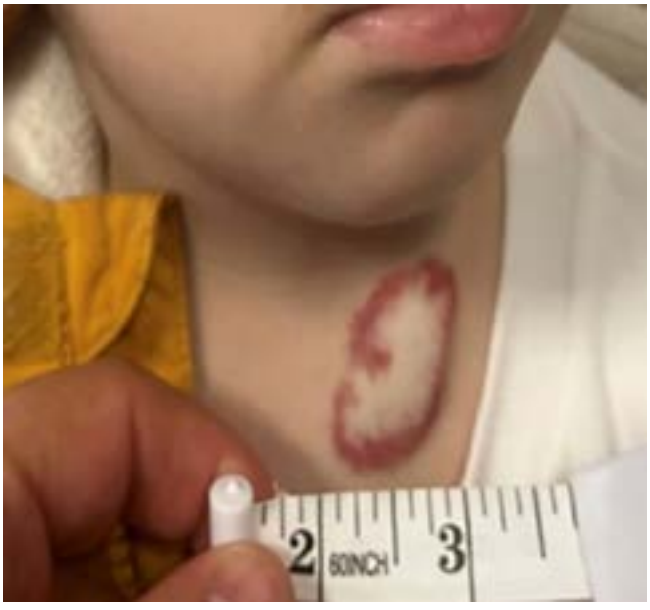

Figure 2. It is observed that the total lesion involution rate is close to 70_ in the 6th month of treatment

A unique case involved a 3-year-old male patient who had applied to an external center with a preliminary diagnosis of an 844 cm right gluteal IH when he was 9 months old. (Fig. 7) Since the typical hemangioma appearance was not

Figure 3. A 3-month-old girl patient had an IH of 3*4*4cm in size, localized in the parieto-frontal region of the head, and propranalol treatment was started with a dose of 2mgkgday, and almost complete involution was detected at the end of the 6th month

Figure 4. A 3-month-old girl patient had an IH of 3*4*4cm in size, localized in the parieto-frontal region of the head, and propranalol treatment was started with a dose of 2mgkgday, and almost complete involution was detected at the end of the 6th month

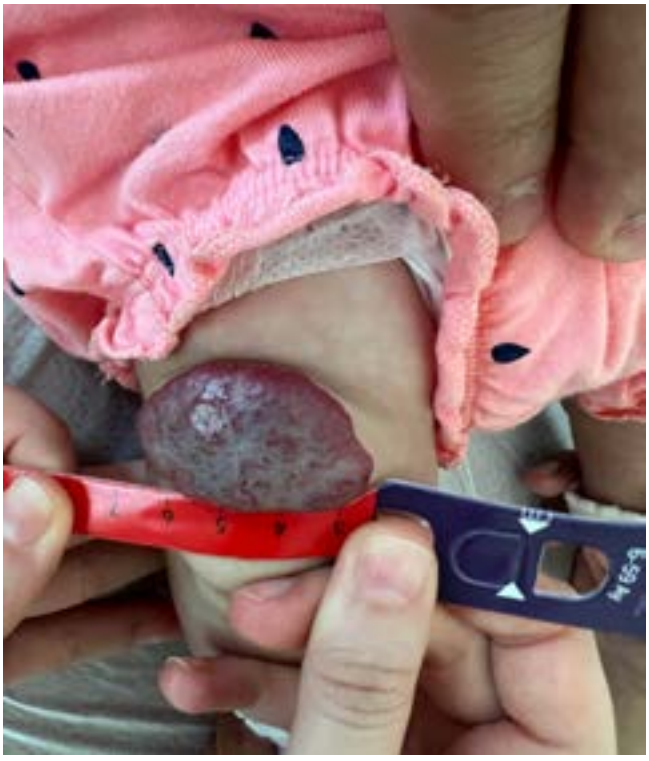

Figure 5. In a 5-month-old male patient, propranalol treatment was started with a dose of 2mgkgday for IH with a size of 4*3*4cm localized on the right leg, and images of the patient with significant involution at the end of the 6th month were presented

Figure 6. In a 5-month-old male patient, propranalol treatment was started with a dose of 2mgkgday for IH with a size of 4*3*4cm localized on the right leg, and images of the patient with significant involution at the end of the 6th month were presented

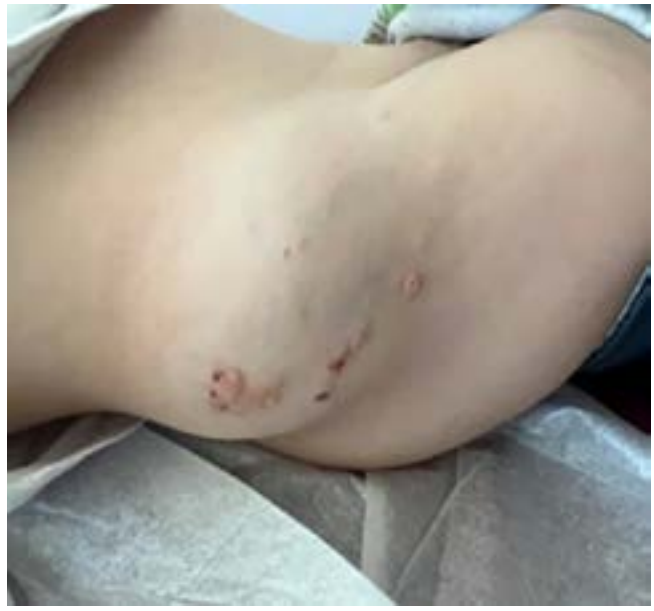

Figure 7. 8*4*4 cm right gluteal venous-lymphatic malformation in a 3-year-old male patient

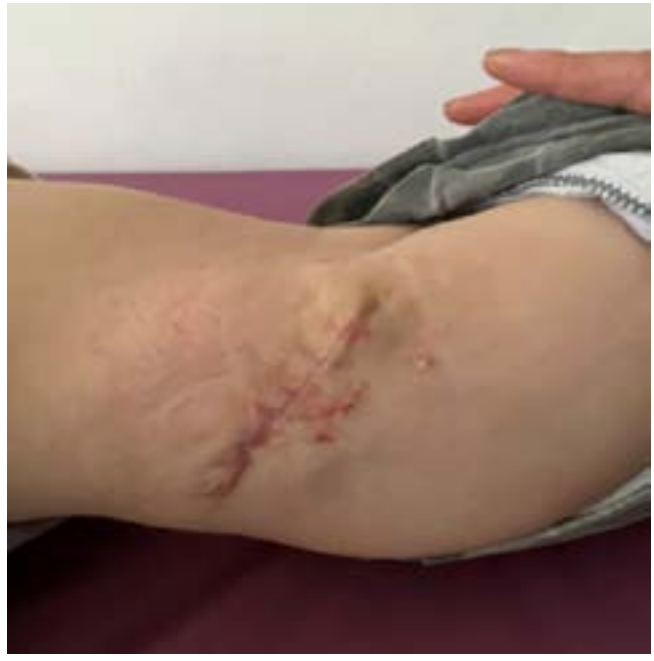

Figure 8. Visual image after surgical excisional surgery performed on the patient with the decision of the tumor council

present, magnetic resonance (MR) imaging was performed. The opinion of the radiology department was obtained, and it was reported as an infantile hemangioma.

For this reason, this patient was started on oral propranolol in the same center, and since there was no shrinkage in the 9–12 month follow-up, the patient was brought to our clinic by his family. It was evaluated as a venous-lymphatic malformation after the color Doppler USG performed on the patient and the re-interpretation of the previous MRI images with the pediatric radiologist. The patient underwent excisional surgery with the decision of the tumor council. The pathology report confirmed venous-lymphatic malformation. The disease was not detected again in the 12-month follow-up period (Fig. 8).

DISCUSSION

Hemangiomas are the most common benign tumors in infancy.[7] Although the majority have little impact on childhood health, some head and genital hemangiomas can progress to a problematic status. These hemangiomas require intervention to control growth and complications to prevent functional and cosmetic deformities. Propranolol has recently been found to reduce the size of hemangiomas during the proliferative phase of IH development.[8] The mechanism of action and pathophysiology behind this discovery still remain unclear. Theories suggesting that propranolol affects hemangioma growth through the induction of apoptosis and anti-angiogenic activity are gaining support.

However, several case studies have provided evidence of the dramatic effect of propranolol on massive, proliferating, life-threatening, and involved lesions.[9] Propranolol has been used for decades to treat hypertension, ischemic heart disease, arrhythmias, endocrine and neurological disorders, and eye disorders. Although it is used, its safety and effectiveness in pediatric patients have not been fully established. The safety and efficacy profile needs to be strengthened with new clinical studies such as ours.

Other treatments for complicated IH include systemic corticosteroids, vincristine, interferon alpha, cyclophosphamide, and surgical excision, all of which carry significant risks. Propranolol is a non-selective beta blocker. It can antagonize both β1 and β2 receptors.[10–12] These receptors, when activated by epinephrine or norepinephrine, result in a variety of actions in a wide range of tissues. The responses have been studied much better in adults than in children. By blocking these receptors in the liver, where glycogen phosphorylase is activated, and in the heart, where calcium flow and retention increase, effects such as bradycardia, hypotension, and hypoglycemia may occur. Clinical signs of these adverse effects include drowsiness, restlessness, difficulty breathing, cool and moist skin, delayed capillary refilling, and decreased appetite.[13–15]

Orally administered propranolol shows significant first-pass metabolism in adults, with peak absorption in 1–3 hours, although data in children are sparse. The half-life in adults is reported to be between 3.5 and 6 hours, but effects often last longer than expected. The mechanism of action of beta-blockers in the treatment of hypertension, ischemic heart disease, arrhythmias, endocrine and neurological disorders, eye disorders, as well as IH, is unclear. Effects of propranolol on the placenta have been demonstrated when used to treat preeclampsia.[16] Perhaps beta blockers induce apoptosis by antagonizing Glut-1 receptors or act in other ways to inhibit the growth of IHs.[17]

The pharmacologically optimal dosing range for propranolol is every 6 hours, but compliance is easier if the drug is given every 8 to 12 hours. Babies admitted to our hospital clinic for IH treatment are first given a dose of 2 mg/kg/day, divided into 2 doses per day.[18] Vital signs and blood sugar are monitored 1 hour after each dose, and this time corresponds to the period of peak absorption. This is equivalent to the dose of 2.0 mg/kg/day, which is the dose used in most patients by Leaute-Labreze et al.[10] Maximum daily doses of up to 5.0 mg/kg have been reported for infants with arrhythmias, but the risk-versus-benefit ratio of higher doses for infants with IH is unclear.[19]

In 4 cases that responded poorly to treatment and had a low involution rate despite 3 months of routine dose treatment, 3.0 mg/kg/day propranolol solution was given orally. In these patients, a significant response was obtained, with almost complete involution starting from the 1st month. In this respect, a dose of 3.0 mg/kg/day can also be selected and tried with close monitoring in treatment-refractory cases.

As in our cases, we recommend a routine dose of 2 mg/kg/day in infants aged 6 weeks to 3 months, with vital signs and blood glucose checked 1 hour after the first dose. The use of propranolol oral solution is considered more reliable for this age group in terms of ease of use and high safety profile. It can be used safely for up to 6 months in patients with stable vital signs and blood sugar.

Przewratil et al.[20]'s study reported that propranolol treatment in IHs inhibited angiogenesis and induced apoptosis. To investigate this claim, they analyzed serum and tissue profiles of VEGF and VEGFR1/2 in patients treated with propranolol. In conclusion, this study addressing mRNA-mediated VEGF and VEGFR1 expression reported that propranolol has anti-angiogenic properties. This provides evidence of good response rates with propranolol in the treatment of IH.

In our IH cases, we showed that the dose of 2 mg/kg/day had the least side effects and was within the safety limits. However, further studies may be needed to determine safety intervals for dose increases to maximize effectiveness and faster response to treatment.

Many vascular malformations can be mistakenly evaluated as IH by general pediatricians and sometimes even pediatric oncologists. Therefore, to confirm the diagnosis, superficial USG/color Doppler USG with a pediatric radiologist should be performed. If necessary, further examination should be conducted before starting treatment.

One case in our study, a 3-year-old male patient, was admitted to an external center with a pre-diagnosis of IH with an 844 cm right gluteal lesion (Fig. 7). Magnetic resonance (MR) imaging was performed and reported as IH by the radiologist because it did not have the typical hemangioma appearance. For this reason, this patient was started on oral propranolol in the same center, and since there was no shrinkage in the 9–12 month follow-up, the patient was brought to our clinic by his family. It was evaluated as a venous-lymphatic malformation after the color Doppler USG performed on the patient and the re-interpretation of the previous MRI images with the pediatric radiologist. The patient underwent excisional surgery with the decision of the tumor council. The pathology report confirmed venous-lymphatic malformation. The disease was not detected again in the 12-month follow-up period (Fig. 8).

CONCLUSION

In conclusion, in this study addressing mRNA-mediated VEGF and VEGFR1 expression, propranolol was reported to have anti-angiogenic properties. Propranolol is suggested to be very effective in IHs of all volumes and locations in the literature. Although its use is highly recommended between 6 weeks and 3 months, in our study, it was observed that it was also very effective in older infants aged 6 months to 24 months.

However, some cases of venous-lymphatic malformation are misdiagnosed as IH and perceived as refractory to treatment. The diagnosis of infantile hemangioma must be confirmed by an experienced pediatric radiologist, and treatment must be started afterward. Propranolol treatment should be started first in cases that show rapid growth and are especially likely to result in functional disorders. If propranolol is unresponsive and surgery is possible, surgery should be performed; if surgery is not possible, other treatment options should be evaluated.

Disclosures

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Ethics Committee Approval: The study was approved by the University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (No: 4385, Date: 30/04/2024).

Authorship Contributions: Concept: H.A.S., Ö.T., M.Ö.; Design: H.A.S.; Supervision: H.A.S.; Materials: H.A.S., Ö.T., M.Ö.; Data Collection or Processing: H.A.S., Ö.T., M.Ö.; Analysis or Interpretation: H.A.S., Ö.T., M.Ö.; Literature Search: H.A.S., Ö.T., M.Ö.; Writing: H.A.S.; Critical review: H.A.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Informed Consent: Consent for publication was obtained from the patients' parents. Patients' parents gave informed written consent for their personal or clinical details, along with any identifying images, to be published in this study.

Use of AI for Writing Assistance: Artificial intelligence (AI) supported technologies (such as Large Language Models [LLM], chatbots or image generators, ChatGPT) were not used in the preparation of this study.

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