Research Article ISSN 2833-0390

International Journal of Research in Oncology

Characteristics and Therapeutic Approaches to Infantile Hemangioma: A Single Center Experience

Özlem Terzi[1]* and Rawan Alkhabbaz[2]

[1]*Department of Pediatric Hematology and Oncology , Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey.*

[2]*Department of Pediatrics, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey.*

***Correspondence:**
Özlem Terzi, Department of Pediatric Hematology and Oncology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Istanbul, Health Science University, Turkey, Tel: 0090-555 786 77 70.

Received: 14 Jul 2024; **Accepted:** 12 Aug 2024; **Published:** 20 Aug 2024

Citation: Özlem Terzi, Rawan Alkhabbaz. Characteristics and Therapeutic Approaches to Infantile Hemangioma: A Single Center Experience. Int J Res Oncol. 2024, 3(3): 1-5.

ABSTRACT

Introduction: *Infantile hemangiomas are the most common benign vascular tumors in childhood.*

Materials and Methods: *We report our experience with 170 patients with IHs.*

Results: *The median age was 6 months and the male/female ratio was 58:112. 81% of the IHs were single site and the most common site was the head and neck region. Median follow-up was 6 months (1-11 months). 98 of our patients were treated with oral propranolol and 43 of them showed visible improvement (>30% reduction). Complications such as bleeding and/or ulceration were seen in 9 of the patients, oral propranolol was successful in complicated IHs.*

Conclusion: *Most IHs resolve spontaneously, but complications may occur. Propranolol alone is an effective treatment option for both IH and complications.*

Keywords

Infantile haemangioma, Oral propranolol, Topical timolol maleate, Vascular anomalies.

Introduction

Infantile hemangiomas result from the rapid division of endothelial cells. They are the most common vascular tumors in childhood. Infantile hemangiomas occur in approximately 4% of children [1]. IH is more common in low birth weight infants, female newborns, multiple gestations, pregnant women on progesterone therapy, and positive family history [1,2]. Studies have also suggested that maternal smoking, advanced maternal age, *in vitro* fertilization, Caucasian race, amniocentesis or chorionic villus sampling, and factors associated with placental insufficiency increase the risk of developing IH [1].

The pathogenesis of IHs is not fully understood. The main cell of origin of IHs has been postulated to be endothelial progenitor cells derived from the chorionic villi of the placenta, supported by the common expression of placenta-associated antigens such as glucose transporter protein-1 (GLUT-1), merosin, FcgRII, and Lewis Y antigen, which are specifically expressed by chorionic villi [3]. The expression of GLUT-1 at all stages of progression is unique to IHs among other vascular tumors and malformations [3], as is their life cycle, which mirrors that of the placenta [4]. Vascular endothelial growth factor-A (VEGF-A), which is involved in angiogenesis, may be an important driver of IH proliferation and may partially justify the response to corticosteroids and propranolol [5]. VEGF-A and GLUT-1, as well as an insulin-like growth factor, are downstream targets of hypoxia-inducible factor-1alpha [5]. This may explain the increased risk of IH after chorionic villus sampling during pregnancy (4). The renin-angiotensin system appears to contribute to angiotensin II, which indirectly promotes angiogenesis. In addition, the development of IHs has been reported to be associated with genetic factors located on chromosome 5q [6].

The infantile hemangioma (IH) is minimally visible at birth (as a pale or pink macular lesion or small red spots) and enters the rapid acute proliferative phase in the first weeks of life. All IHs, whether superficial or deep, exhibit a biological behavior consisting of 3 stages (proliferative phase, 8-12 months; involutional phase, 1-12

years; and final phase, remnant phase) [3,7]. The most rapid growth occurs between 1 and 3 months of age, and growth usually reaches maximum size at 9-12 months [8,9]. At this point, it reaches a plateau, stabilizes, and begins to involute; beginning around 12 months of age, a change in the color and texture of the IH marks the involution phase, where it becomes more violaceous-gray, softer, and more compressible [1]. IH often results in fibrofatty tissue and usually resolves spontaneously [10]. It has been reported that 30% of infantile hemangiomas regress completely by 3 years of age and 75%-90% by 7 years of age [11,12]. Sometimes regression does not occur and growth continues [13]. However, it is important to remember that the proliferation, involution, and remnant phases of each lesion vary in duration and transition between phases [3].

Hemangioma precursors and early proliferating lesions can sometimes be confused with other vascular lesions. Congenital hemangiomas proliferate in utero (thus may be detected on prenatal ultrasound), may be symptomatic prenatally due to high flow, and are present at birth. Postnatally, a congenital hemangioma may either enter a phase of rapid involution, partially involute, or maintain its volume without further enlargement. There are congenital hemangiomas with postnatal growth, but these appear to be rare. In venous and lymphatic malformations, although the lesion may change slightly in size and shape as the child grows, it usually remains in the same anatomic location. Hemangiomas undergo regulated stages of proliferation and gradual involution [14]. A nonulcerated IH is usually not painful. Venous malformations may cause chronic pain and discomfort due to venous stasis, with acute exacerbations caused by the formation of small thrombi within the lesion. Plexiform neurofibroma, infantile fibrosarcoma, dermatofibrosarcoma protuberans, rhabdomyosarcoma, nasal glioma, telangiectasia, dermoid cyst, and infantile myofibroma are other lesions that rarely mimic infantile hemangioma. The majority of IHs resolve spontaneously and do not require treatment. The main goals of patient management in infantile hemangioma are to prevent life- or function-threatening complications, to treat ulceration, to protect from permanent structural disorders, and to reduce the psychological distress of the patient and the family [13,15-18]. The currently available treatment regimens include oral medications, topical medications, injectable medications applied, and laser and surgical options. Among them, oral beta blockers have shown excellent curative effects. Surgery is not a priority for IHs that are expected to resolve spontaneously or can be controlled with medical treatment. Sometimes, surgery is performed for reconstruction after the residual adipose fibrous phase.

In this study, we aimed to evaluate the clinical characteristics, treatment indications, complications, and treatment response of patients diagnosed with IH.

Materials and Methods

The records of 160 patients admitted to our pediatric oncology outpatient clinic between May 1, 2023 and May 1, 2024 with a diagnosis of IH and hemangioma were retrospectively analyzed. Patients aged 0-24 months with IH were selected for this study. Patients were managed by a multidisciplinary team including a pediatric oncologist, pediatric cardiologist, pediatric ophthalmologist, and pediatric dermatologist. Age at diagnosis, sex, type, location, number, complications, treatment indications, treatment modalities, treatment responses, and follow-up periods were recorded. Patients admitted to our center for non-IH vascular malformations were excluded. Patients older than 24 months of age were excluded from the study. Patients younger than 6 months with superficial IH were treated with topical propranolol 0.5% solution twice daily at a dose of one drop. Among these patients, oral propranolol treatment was switched in those whose IHs tended to grow and in those who developed bleeding and ulceration.

Propranolol was the first-line treatment for head and neck IHs, especially those with periorbital localization (risk of visual impairment) and perioral localization (nutritional problems), bleeding, infection, ulceration, and diameter greater than 3 cm. A careful history was taken and a detailed physical examination was performed before starting treatment. Contraindications and history of risk factors such as cardiac arrhythmia, reactive airway disease, hypotension, and hypoglycemia were assessed. Patients with any of these risk factors were excluded. All patients underwent a pediatric cardiology evaluation with echocardiography at baseline. In infants less than two months of age, the drug was administered orally in two doses, starting with a low dose of 0.5 mg/kg/day and gradually increasing to 2 mg/kg/day, and all patients were hospitalized for 24 hours. The first follow-up visit was 7-10 days after discharge. The drug dose was started at 2 mg/kg/day in patients over two months of age. The dose was adjusted according to the child's weight at each outpatient visit. Evaluation included physical examination and photographic documentation at each visit. Serial photographs were taken throughout treatment. Patients were also evaluated for propranolol-related adverse events by medical history and physical examination.

Periorbital hemangiomas were followed by ophthalmology, while patients with ulcerated IH were followed by dermatology. Treatment was discontinued after complete resolution of the IH. Drug treatment was reduced to a half daily dose for four weeks. In case of rebound, the dose was doubled again daily. Patients were called for follow-up two months after discontinuation of treatment. The study protocol was approved by the Institutional Ethics Committee (2024-01-02). Written informed consent was obtained from the patients' parents and/or legal guardians. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Statistical analysis was performed with SPSS version 22.0 (IBM Corp., Armonk, NY., USA). Descriptive data are expressed as median (min-max) or number and frequency, as appropriate.

Results

A total of 170 patients with IH were followed up in our pediatric oncology outpatient clinic. The median age at presentation was 4 months (0-24 months) and the male/female ratio was 58:112.

While 81% of the patients (137/170) had IHs in a single region, the remaining 19% had IHs in other regions. The most common

site of IHs was the head and neck region (89/170). Of the head and neck lesions, 8 were around the eyes, 1 in the inner part of the ear, and 1 in the oral mucosa. Only 1 patient had visual impairment, and the patient with ear involvement had no hearing problem. Oral mucosal hemangioma did not cause any eating problems. Other sites of hemangioma involvement were extremities (26/170), trunk (25/170), back (20/170), genital region (4/170), gluteal region (6/170).

Patient follow-up was performed in 56% (96/170) of all patients, 44% (74/170) of the patients did not return to the outpatient clinic for follow-up after the initial presentation. The median follow-up was 6 months (1-11 months). IH resolved completely in 7 patients treated with oral propranolol, improved by more than 50% in 13 patients, and improved by 30-50% in 23 patients. Topical timolol maleate was the first choice of treatment in 27.6% (47/170) of patients, IH resolved completely in 3 patients treated with timolol maleate and improved by more than 30% in 4 patients. Both timolol maleate and dideral were used in the treatment of 4 patients. In 23 patients, the oral propranolol treatment was changed because the IH tended to increase or remain constant, and the treatment response was a regression of more than 30% in more than half of these patients after the drug change. Three patients had complications during propranolol treatment; 1 patient had sleep disturbance, agitation; 2 patients had diarrhea. Hypoglycemia, bradycardia, and hypotension were not observed in any patient. Five patients vomited oral propranolol tablets and were treated with oral propranol suspension. Evaluation of improvement was based on visual assessment by parents and clinicians, physical examination, documentation of photographs, and measurement of superficial skin hemangiomas. Complications of IHs were observed in 9 of 170 patients (5%) and included ulceration in 5 patients, bleeding in 3, and both ulceration and bleeding in 1. These 9 patients were successfully treated with oral propranolol. In patients who developed complications, IHs were located in the genital region in 3 patients, the gluteal region in 3 patients, the occipital region in 2 patients, and the neck region in 1 patient.

Discussion

Although most IHs are expected to resolve spontaneously, the management approach varies from patient to patient. The complication rate may have decreased with the introduction of propranolol in the treatment of IHs after 2008 [19,20]. The mechanism of action of propranolol is thought to be due to vasoconstriction, inhibition of angiogenesis, and induction of apoptosis [19,20]. The dose of propranolol can be increased to 2-3 mg/kg/day and treatment can be continued for 12-18 months [21,22]. In our center, propranolol treatment was increased to 3 mg/kg/day depending on the patient's condition and continued for up to 12 months.

The most common sites of involvement of hemangiomas are the trunk and head and neck region, but they can occur on any skin or mucosal surface. According to our data, the most common site of hemangiomas was the head and neck region.This may be due to cosmetic concerns of families regarding IHs occurring in these regions. 70-90% of hemangiomas are found alone [23,24]. Similarly, in our study, 81% of our cases had IHs in a single region. IHs are usually small and resolve spontaneously without intervention, but in some cases they can cause permanent disfigurement and functional impairment. Up to 69% of cases leave permanent residual skin changes consisting of involution, telangiectasis, fibrofatty tissue, atrophy, erythema, hypopigmentation, or potentially scarring if ulceration occurs [15]. Ulceration is the most common complication associated with IHs, occurring in approximately 10% of cases. In our study, ulceration/bleeding occurred in 5% of cases and was successfully treated with propranolol. It can cause pain, infection, bleeding, disfigurement and scarring [25]. The most common sites are the head and neck, anogenital, and intertriginous regions, which are more prone to trauma, contamination, and therefore risk of ulceration and minor bleeding [25,26]. The most complicated hemangiomas in our study were in the glandular region (gluteal, genital). It can be assumed that complications occur more frequently in these areas, which are exposed to urine and feces contact in young infants.

Functional deficits are most common in IH of the head, neck, and around natural orifices. Periocular hemangiomas are usually small, but the mass effect on the cornea can cause astigmatism, strabismus, and ptosis in about one-third of affected patients. Amblyopia may progress to permanent visual impairment. This is more likely to occur when the upper eyelid is involved [27]. In our study, 9 patients had upper eyelid hemangiomas; only 1 of these patients had visual impairment; this may be because oral propranolol treatment was started immediately for IHs occurring in the eye. Perioral IHs may cause feeding and swallowing difficulties [28]. For example, IHs on the tip of the nose and lip may leave residual skin changes.

Large IHs (≥2 cm in size) may cause scarring and other permanent sequelae [24]. Scalp IHs may cause alopecia, and breast IHs may cause breast asymmetry in female patients [24]. Nipple hemangiomas cause problems in girls. These lesions may involve the nipple and residual masses may cause breast asymmetry. Early surgical intervention is not recommended because it may interfere with normal breast development. In a 14-year-old patient who could not be included in the study because she was too old, a nipple hemangioma that could not be treated at a young age was found to cause breast asymmetry, with one breast being less than half the size of the other.

Various approaches including steroids, oral propranolol, topical timolol maleate, and laser therapy are used in the treatment of infantile hemangioma [29,30]. Propranolol is the first-line treatment for IHs [31]. Propranolol is a lipophilic, non-selective β-blocker. Its mechanism of action in hemangiomas can be summarized as vasoconstriction, apoptosis, and inhibition of angiogenesis. Improvement has been observed within at least three months after initiation of propranolol treatment [23,24]. Propranolol was the first-line treatment for head and neck IHs, especially those with periorbital localization (risk of visual impairment) and perioral localization (nutritional problems), bleeding, infection, ulceration,

and diameter greater than 3 cm. In the studies, the response to oral propranolol treatment was reported to be 84.6-96.9% [32,33]. Ninety-eight of our patients were treated with oral propranolol and 43 of them showed visible improvement (>30% reduction), and complete recovery was observed in patients who developed complications. Oral propranolol treatment of the remaining patients is ongoing, and a clearer answer to the treatment response can be given in long-term follow-up.

Topical timolol maleate is a safe and effective treatment and can be used as an alternative to oral propranol [34]. In addition, the use of timolol maleate in combination with laser has been reported to be effective in the treatment of deep IHs [35]. In our study, timolol maleate was not used in complicated cases, but was used in the treatment of superficial hemangiomas and was partially beneficial.

The limitations of our study are the limited number of cases and the short follow-up period of the patients. Another limitation is that the treatment response of patients who did not return for follow-up is not known.

In conclusion, IHs are the most common benign tumors of childhood, with the majority occurring in the head and neck region. For complicated IHs, oral propranolol is the first-line treatment option because of its safety and efficacy.

References

1. AI RB, DF S, Wargon O, et al. Infantile hemangioma. Part 1: Epidemiology, pathogenesis, clinical presentation and assessment. J Am Acad Dermatol. 2021; 85: 1379-1392.
2. Ding Y, Zhang JZ, Yu SR, et al. Risk factors for infantile hemangioma: a meta-analysis. World J Pediatr. 2020; 16: 377-384.
3. North PE, Waner M, Mizeracki A, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol. 2001; 137: 559-570.
4. Munden A, Butschek R, Tom WL, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. Br J Dermatol. 2014; 170: 907-913.
5. Holland KE, Drolet BA. Approach to the Patient with an Infantile Hemangioma. Dermatol Clin. 2013; 31: 289-301.
6. Berg JN, Walter JW, Thisanagayam U, et al. Evidence for loss of heterozygosity of 5q in sporadic haemangiomas: are somatic mutations involved in haemangioma formation?. J Clin Pathol. 2001; 54: 249.
7. Frieden IJ, Haggstrom AN, Drolet BA, et al. Infantile hemangiomas: current knowledge, future directions: proceedings of a research workshop on infantile hemangiomas, April 7-9, 2005, Bethesda, Maryland, USA. Pediatr Dermatol. 2005; 22: 383-406.
8. Leaute Labreze C, Harper JI, Hoeger PH. Infantile haemangioma. Lancet. 2017; 390: 85-94.
9. Chang LC, Haggstrom AN, Drolet BA, et al. Growth Characteristics of Infantile Hemangiomas: Implications for Management. Pediatrics. 2008; 122: 360-367.
10. Wildgruber M, Sadick M, Müller Wille R, et al. Vascular tumors in infants and adolescents. Insights Imaging. 2019; 10: 30.
11. Shields JA, Shields CL. Eyelid, Conjunctival, and Orbital Tumor: An Atlas and Textbook. Lippincott Williams Wilkins. 2008: 132-157.
12. Haik BG, Karcioglu ZA, Gordon RA, et al. Capillary hemangioma (infantile periocular hemangioma). Surv Ophthalmol. 1994; 38: 399-426.
13. Yildirimcakar D, Demirsoy U, Azizoglu M, et al. Evaluation of Clinical Properties and Treatment Responses of Infantile Hemangioma. J Drugs Dermatol. 2020; 19: 1156-1165.
14. Lanzkowsky's manual of pediatric hematology and oncology. 2021.
15. Luu M, Frieden IJ. Haemangioma: clinical course, complications and management. Br J Dermatol. 2013; 169: 20-30.
16. Colmant C, Powell J. Medical Management of Infantile Hemangiomas: An Update. Paediatr Drugs. 2022; 24: 29-43.
17. Hoeger PH, Harper JI, Baselga E, et al. Treatment of infantile haemangiomas: recommendations of a european expert group. Eur J Pediatr. 2015; 174: 855-865.
18. Smithson SL, Rademaker M, Adams S, et al. Consensus statement for the treatment of infantile haemangiomas with propranolol. Australas J Dermatol. 2017; 58: 155-159.
19. Léauté Labrèze C, Hoeger P, Mazereeuw Hautier J, et al. A Randomized, Controlled Trial of Oral Propranolol in Infantile Hemangioma. N Engl J Med. 2015; 372: 735-746.
20. Mariani LG, Ferreira LM, Rovaris DL, et al. Infantile Hemangiomas: Risk Factors for Complications, Recurrence and Unaesthetic Sequelae. An Bras Dermatol. 2022; 97: 37-44.
21. Solman L, Glover M, Beattie P, et al. Oral Propranolol in the Treatment of Proliferating Infantile Haemangiomas: British Society for Paediatric Dermatology Consensus Guidelines. Br J Dermatol. 2018; 179: 582-589.
22. Tiemann L, Hein S. Infantile Hemangioma: A Review of Current Pharmacotherapy Treatment and Practice Pearls. J Pediatr Pharmacol Ther. 2020: 25; 586-599.
23. Darrow DH, Greene AK, Mancini AJ, et al. Diagnosis and Management of Infantile Hemangioma. Pediatrics. 2015; 136: 1060-1104.
24. Krowchuk DP, Frieden IJ, Mancini AJ, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics. 2019; 143: 20183475.
25. Faith EF, Shah S, Witman PM, et al. Clinical features, prognostic factors, and treatment interventions for ulceration in patients with infantile hemangioma. JAMA Dermatol. 2021; 157: 566-572.

26. Mariani LG, Ferreira LM, Rovaris DL, et al. Infantile hemangiomas: risk factors for complications, recurrence and unaesthetic sequelae. Anais brasileiros de dermatologia. 2022; 97: 37-44.
27. Zhao J, Huang AH, Rainer BM, et al. Periocular infantile hemangiomas: Characteristics, ocular sequelae, and outcomes. Pediatr Dermatol. 2019; 36: 830-834.
28. Solman L, Glover M, Beattie PE, et al. Oral propranolol in the treatment of proliferating infantile haemangiomas:British Society for Paediatric Dermatology consensus guidelines. Br J Dermatol. 2018; 179: 582-589.
29. Saka B, Téclessou J, Akakpo S, et al. Traitement des hémangiomes infantiles au Togo Treatment of infantile hemangioma in Togo. Ann Dermatol Venereol. 2018; 145: 790-792.
30. Dávila Osorio VL, Iznardo H, Roé E, et al. Propranolol-resistant infantile hemangioma successfully treated with sirolimus. Pediatr Dermatol. 2020; 37: 684-686.
31. Terzi Ö, Arslantaş E, Baş CN, et al. Oral Topical Maleat or Oral Propranolol Treatment for Infantile Hemanjiomas: Clinical Analysis of 403 Patients. Sanamed. 2023; 18: 133-139.
32. Ainipully AM, Narayanan SK, Vazhiyodan AP, et al. Oral propranolol in infantile hemangiomas: Analysis of factors that affect the outcome. J Indian Assoc Pediatr Surg. 2019; 24: 170-175.
33. Zhang L, Wu HW, Yuan W, et al. Propranolol therapy for infantile hemangioma: our experience. Drug Des Devel Ther. 2017; 11: 1401-1408.
34. Jha AK, Kumar P, Anand V. Topical Timolol: A novel approach in infantile hemangioma. Skinmed. 2015; 13: 429-431.
35. Sun L, Wang C, Cao Y, et al. Fractional 2940-nm Er: YAG laser-assisted drug delivery of timolol maleate for the treatment of deep infantile hemangioma. J Dermatolog Treat. 2021; 32: 1053-1059.