



## Excellent Response of Infantile Hemangioma with Oral Propranolol: A Case Report

Armyta Denissafitri, Riezky Januar Pramitha, Yuri Widia, Irmadita Citrashanty<sup>ID</sup>, Iskandar Zulkarnain, Sawitri

*Department of Dermatology and Venereology Faculty of Medicine*

*Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia*

### ABSTRACT

**Background:** Infantile hemangioma (IH) is the most common benign tumor in infancy. Most IHs resolve spontaneously and do not require treatment. Therapeutic intervention is necessary for life-threatening IH, tumors posing functional risks, ulceration, and severe anatomic distortion, especially on the face. Beta-blockers, most specifically propranolol, have been shown to induce involution of IH, which should be administered as early as possible to avoid potential complications. **Purpose:** To report a case of IH with visual impairment treated successfully using oral propranolol. **Case:** A 4-month-old girl weighing, 6.3 kg, with redness plaques on the right face since 3 weeks after birth. The lesions rapidly increased in size within 2 months, and the lesions on her right eyelid made it difficult to open her right eye. Dermatological examination showed erythematous plaques, compressible and varying in size and ptosis. The patient was diagnosed with periocular infantile hemangioma and was given oral propranolol therapy with an initiated dose 3x1 mg. The dose was increased gradually. The lesions were significantly decreased and she could open her right eye normally after 5 months of propranolol therapy. **Discussion:** Some cases of IH require early treatment. Early treatment is indicated for IH causing functional impairment. The use of propranolol in the management of IH is very effective in the reduction of the lesions and has minimal side effects. **Conclusion:** Early diagnosis and intervention with propranolol for IH play an important role in determining the optimal outcomes.

**Keywords:** Infantile hemangioma, treatment, propranolol.

Correspondence: Sawitri, Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jl. Prof. Dr. Moestopo No. 6-8 Surabaya 60131, Indonesia. phone: +62315501609, e-mail: [sawitri@fk.unair.ac.id](mailto:sawitri@fk.unair.ac.id).

| Article info |

Submitted: 19-01-2021, Accepted: 09-12-2021, Published: 30-11-2022

This is an open access article under the CC BY-NC-SA license <https://creativecommons.org/licenses/by-nc-sa/4.0/>

### BACKGROUND

Infantile hemangioma (IH) is the most common benign vascular tumor of infancy. IH arises in the first few weeks of life, then displays a period of active growth followed by spontaneous involution.<sup>1,2</sup> Most IHs are uncomplicated, do not require intervention, and regress spontaneously.<sup>3</sup> If IH is located in an anatomically sensitive area, such as lesions around the eye, nasal tip, mouth, in the airway, gastrointestinal tract, liver, or if rapid proliferation leading to disfigurement is expected, or if there are concerns for potential functional impairment, then additional workup and treatment are indicated.<sup>4,5</sup>

IHs are identified in approximately 1–2.5% of newborns, although an incidence of 10% in the first year of life has been typically quoted.<sup>1</sup> A retrospective

study period from 2008–2017 at the Dermatology and Venereology Outpatient Clinic, Dr. Soetomo General Academic Teaching Hospital Surabaya, there were 84 (0.04%) IH patients, and they made up 0.69% of the total patients of the Pediatric Dermatology Division of the Dermatology and Venereology Department outpatient clinic of Dr. Soetomo General Hospital Surabaya. Between 2008 and 2017, there were 60 (71.43%) patients aged less than one year. Besides, there were 53 (63.1%) female patients and 31 male patients (36.9%). The most common IH location was the facial region in 49 patients (58.33%).<sup>6</sup>

Continuous exploration and optimization of therapeutic regimens have been carried out in recent years for IH. Many curative therapeutic regimens have emerged and been applied in clinical practice,

including oral medications, injectable medications, topical medications, laser therapy, and surgical treatment.<sup>4,7</sup> Systemic medical therapies are indicated to prevent the development of morbidities associated with both proliferative and involuting/involved phase morbidities. The goal of medical therapies is to prevent or limit IH proliferation to decrease the risk of ulceration/bleeding, or the subsequent disfigurement that may result without intervention.<sup>5</sup>

Propranolol is a non-selective beta-adrenergic receptor blocker and representative of conventional drugs that have been used in children for the treatment of cardiac conditions for decades.<sup>8</sup> The efficacy of propranolol in IH was reported serendipitously by Léauté-Labrèze *et al.* in 2008, when the use of propranolol in their patients for hypertrophic cardiomyopathy led to a dramatic improvement in patient's hemangioma.<sup>9</sup> Propranolol is the only medication approved by the United States Food and Drug Administration (FDA) for the treatment of complicated IH.<sup>4,8</sup>

## CASE REPORT

A 4-months-old girl was brought by her mother to the Dermatology Outpatient Clinic of Dr. Soetomo General Hospital Surabaya. Since 3 weeks after birth, the chief complaint has been redness plaques on the right upper eyelid and a small area of the forehead. The red marks started on her right upper eyelid, spread to her temple and forehead. The lesions rapidly increased in size and became wider within 2 months, and the lesions on her right eyelid made it difficult for her to eye normally. The patient had been taken to Lamongan

Hospital and given a mixed ointment by a dermatologist that had been used for 2 months but there was no improvement.

The patient was born through a caesarean section at full term. The birth body weight was 2700 grams and immunizations were complete for her age. Her mother was 25 years old, this was her first pregnancy and she was healthy during her pregnancy. There was no history of taking traditional medicine. There was no history of the same complaint in her family. The growth and development of the patient were normal.

The physical examination of general status showed her body weight was 6,3 kg, the pulse rate was 115 times per minute, the respiratory rate was 30 times per minute and the body temperature was 36.5°C. Head and neck examinations showed no signs of anemia, cyanosis, icterus, or dyspnea. Thorax, heart, and lungs examination were normal. The abdomen, liver, and spleen were not palpable. The upper and lower extremities showed no edema and were warm on palpation.

Dermatological examination showed multiple erythematous plaques, compressible, varying in size, no ulcer on the frontalis, temporalis, and superior palpebra dextra region (Figure 1). The lesions on her right upper palpebra made it difficult for the patient to open her eye. Laboratory examination revealed hemoglobin was 9.4 g/dL, white blood cells was 8,4000/mm<sup>3</sup>, thrombocytes was 330,000/L, hematocrit was 28,5%. Based on the hemogram examination, ferritin was 270 µg/L, iron was 23 Ug/dl, and total iron-binding capacity was 364 Ug/dl. Blood glucose was 90 mg/dL.



**Figure 1.** Dermatological status before the treatment. A. Multiple erythematous plaques, compressible, varying in size, on the frontalis, temporalis, and superior palpebra dextra region. B. The lesion diameter on the palpebra superior was 3 cm.

Based on the clinical history and physical examination, the patient was diagnosed with periocular infantile hemangioma dextra. The patient was planned to be given oral propranolol treatment and consulted

with the pediatric department to screen for contraindications of the propranolol treatment. The electrocardiogram (ECG) examination revealed sinus tachycardia. The consultation result from the pediatric

department based on anamnesis, physical examination, and laboratory findings, there were no contraindications to giving oral propranolol. The patient was also consulted to the ophthalmology department due to the lesions on the superior palpebra dextra and had a complaint of difficulty opening her right eye, the result was no abnormalities in her eye.

The patient was treated with oral propranolol the initiating dose was 3x1 mg (0,5 mg/kg/day), the propranolol dose was increased gradually by 0,5

mg/kg/day for 5 months, with the last dose was 3x3 mg (1,5 mg/kg/day) for 1 month. Follow-up visit records were reviewed and screened for possible side effects of propranolol. The patient went to the outpatient clinic every month. Her vital signs and blood glucose evaluation was normal. There were rapid size reduction and improvement in the patient's vision after 5 months of oral propranolol treatment. In this case, as long as the patient received oral propranolol, there were no side effects from the drug in the patient.



**Figure 2.** The lesion's progression after oral propranolol treatment. A. First month of treatment, B. Second month of treatment, C. Third month of treatment, D. Fourth month of treatment, E. Fifth month of treatment.

## DISCUSSION

Infantile hemangiomas (IH) are the most common benign tumor of infancy. IHs are unique tumors that proliferate in infancy and eventually involute spontaneously in childhood. IH absence at birth and arising in the first few weeks of life displays a period of active growth, in the vast majority of cases, followed by a period of apparent inactivity and subsequent involution.<sup>1,4</sup>

Several risk factors for IH have been identified. IH is more common in girls (2 to 3:1 ratio), in white, non-Hispanic infants, and infants with low birth weight, especially those weighing less than 2500 g.<sup>4</sup> It increases with decreasing gestational age and is as high as 23% in premature babies smaller than 1000 g birthweight.<sup>2</sup> Other reported risk factors include placental anomalies, preeclampsia, placenta previa, multiple gestation pregnancy, and advanced maternal age.<sup>3,4</sup> It is suitable with this case that it was occurred in girls but for other risk factors were not found in this patient.

The pathogenesis of hemangiomas is still not completely understood.<sup>1</sup> Current understanding suggests that both angiogenesis, the development of new blood vessels from existing blood vessels, and vasculogenesis, the de novo development of blood vessels, are important in IH development.<sup>4</sup> The most likely scenario would involve hypoxic stress as the triggering signal, inducing overexpression of

angiogenic factors such as VEGF via the HIF $\alpha$  pathway. During the growth phase, endothelial cells predominate, resulting in the formation of syncytial masses without a defined vascular architecture. Later, luminesced capillary-like structures appear with multilaminated basement membranes, involving endothelial cells and pericytes. Then, after 2–3 years of age, the infantile hemangioma involutes, the lumina become narrower, and the blood vessels are replaced with a fibrofatty residuum due to the presence of mesenchymal cells with an adipogenic potential. Throughout their development, endothelial cells in infantile hemangioma express a particular phenotype showing positive staining for glucose transporter (GLUT1), LYVE-1, mersin, and antigen Lewis Y.<sup>2</sup>

The precursor IH lesions often appear as a blanched macule, an erythematous or telangiectatic patch with or without a pale halo, a closely packed cluster of bright-red papules, or a blue-tinged bruise-like area.<sup>1</sup> A clinical history of a life cycle marked by characteristic proliferation and involution is critical in the diagnosis of IH. Almost all IHs with a superficial component become apparent in the first month of life, and most will at least double in size within the first 2 months of life.<sup>4</sup> IH enters a period of rapid proliferation in the first few months of age, with maximal growth occurring between 5 and 7 weeks. The early proliferative phase is completed by around 5 months of age, a time when most (up to 80%) of the IH have

completed growth. After proliferation ends, IH may enter a stabilization or plateau phase with eventual spontaneous involution, usually beginning around the first birthday.<sup>8</sup> The involution phase is more variable in length, lasting from months to years. Evidence of involution, often referred to as graying, involves a change to a dull red, then a gray or milky-white color, followed by flattening and softening, which continues through approximately 4 to 5 years of age.<sup>4,8</sup>

The diagnosis of IH is almost exclusively clinical, based on physical examination and clinical history. Clinical history is critical in the diagnosis of IH. Absence at birth or the presence of a nascent IH, often an area of pallor, telangiectasias, or duskininess is characteristic.<sup>4</sup> In this case, the patient has had redness plaques on the right upper eyelids and a little forehead since 3 weeks after birth.

The regression of IH is usually spontaneous after 1 year of age. Sometimes complications may be severe and waiting for a spontaneous involution may cause irreversible functional and aesthetical damage. Treatment is only required for complicated cases.<sup>10</sup> Indications for treatment include life-threatening IH, functional impairment (periocular hemangiomas causing amblyopia, obstructive tumors of the nose or the external auditory channel, ulcerated infantile hemangioma), and disfigurement.<sup>2</sup>

IH in the periocular region deserves special attention as it causes life-long vision-threatening complications.<sup>11</sup> Many IH in the periocular region are small and do not require treatment, although direct compression caused by a deep component of the lesion or secondary to induced ptosis may reshape the globe, resulting in unequal refractive power between the eyes. Periocular IH should be diagnosed early and treated promptly because of its serious complications due to their specific location.<sup>12,13</sup> Ocular complications due to periocular lesions include ptosis, strabismus, telangiectasia, ulceration, scarring, and facial disfigurement, but the most common ocular complication of periocular hemangiomas in infants is visual loss secondary to amblyopia.<sup>14</sup> Specific characteristics that place an infant at a higher risk for amblyopia include an IH size of >1 cm, upper eyelid involvement, associated ptosis, eyelid margin changes, medial location, and segmental morphology or displacement of the globe.<sup>15</sup> Although involution of the lesion is spontaneous and complete in most cases, treatment and early intervention are indicated when lesion growth is rapid and when the infant's vision is compromised.<sup>16</sup>

Beta-blocker have widely established efficacy in IH treatment and a more favourable risk profile compared with prior systemic treatment options.

Propranolol is the only medication approved by the FDA for the treatment of complicated IH. Oral beta-blockers as first-line treatment have revolutionized complicated IH with excellent efficacy and good safety profile.<sup>1,4</sup> Propranolol is highly effective and has been demonstrated to be a well-tolerated medication, with effectiveness in all stages of IH. Positive effects include lightening of color and softening of texture. Treatment duration is determined by a variety of factors, including age, hemangioma location, hemangioma subtype, and age at initiation of therapy.<sup>8</sup>

The proposed mechanism of action of propranolol includes vasoconstriction, inhibition of vasculogenesis, angiogenesis, and induction of apoptosis.<sup>3</sup> The rapid vasoconstriction, which corresponds to the color change from pink to violaceous typically seen in the first 1 to 2 days of therapy. Inhibition of angiogenesis by downregulation of proangiogenic growth factors vascular endothelial growth factor (VEGF) in hemangioma-derived stem cells, basic fibroblast growth factor, and matrix metalloproteinases 2 and 9 seems to correspond to growth arrest. Third, intermediate effects include a reduction in and blockage of proangiogenic factors and finally, after prolonged use, it induces apoptosis of endothelial cells in proliferating phase, which has been proposed to result in the stimulation of IH regression.<sup>14,17</sup>

The propranolol treatment of IH dose is typically started at 1 mg/kg/day in 2 divided doses and increased by 0.5 mg/kg/day increments every 3 to 7 days to a target dose of between 2 and 3 mg/kg/day. Most practitioners use propranolol at 2 mg/kg/day.<sup>4</sup> From the PERDOSKI clinical pathway, the treatment of IH in the proliferation phase using propranolol 3mg/kg/day for 6 months is safe and effective. IH treatment with propranolol started at 2mg/kg/day divided into 3 doses for 6 months has been proven to reduce the size, thickness, and reddish color of the lesion.<sup>18</sup>

The patient was screened for contraindications to the initiation of propranolol at the first outpatient visit. Observed side-effects of propranolol are reversible and usually mild, including sleep alteration (11%), acrocyanosis (5%), gastrointestinal symptoms (3%), asymptomatic transient hypotension, bronchospasm, or bronchiolitis. More severe but rare occurrences of hypoglycaemia, bradycardia, and symptomatic hypotension have been reported. The pretreatment ECG was obtained at the initial visit.<sup>1,19</sup> Of all the potentially serious side effects, hypoglycemia is the most worrisome. Sweating is the only sign of hypoglycemia that is not blocked by a beta-blocker. Sweating may be the most reliable early sign of hypoglycemia to watch for. Routine screening of serum glucose is not indicated

because the timing of hypoglycemia events is variable and unpredictable. Hence, to reduce the risk, propranolol should be administered during daytime hours with a feed just shortly before or after administration and should be discontinued in periods of poor oral intake or illness.<sup>20</sup>In this case, throughout the administration of oral propranolol, there were no side effects from the drug reported.

In this case, the patient received oral propranolol therapy with an initiating dose of 3x1 mg (0,5 mg/kg/day). The propranolol dose was increased gradually to 0,5 mg/kg/day for 5 months, with the last dose being 3x3 mg for 1 month. The lesions were significantly decreased. The dermatological status on the frontal and temporal region revealed telangiectasia and bright erythematous macule. In the superior palpebra dextra, there was a bright erythematous plaque and she could open her right eye normally. In this case, there was an excellent response with only propranolol therapy.

The prognosis of most IHs is excellent. The wide heterogeneity of the condition mandates that prognosis be assessed individually based on location, extent, and any associated complications. Infants with periocular hemangiomas are at risk for anisometropia and amblyopia, which, if untreated, can lead to permanent visual loss. The most favorable prognostic sign to herald normal vision following involution is the absence of asymmetrical refractive error.<sup>1,4</sup>

IH is the most common vascular tumor in infants, appearing in early infancy and spontaneously regressing with time. Clinical presentation may vary, with a minority of lesions causing impairment of vital function, permanent scarring, and/or disfigurement. Propranolol is the first-choice treatment for IH. Early intervention with propranolol for IH was associated with better efficacy. Thus, early recognition of symptoms, diagnosis, and therapy play an important role in determining the optimal outcome of this condition.

## REFERENCES

1. Bruckner AL, Frieden IJ, Powell J. Infantile Hemangiomas. In: Hoeger P, Kinsler V, Yan A, editors. *Harper's Textbook of Pediatric Dermatology*. Oxford: Wiley Blackwell; 2020. p. 1425–39.
2. Léauté-Labrèze C, Harper JI, Hoeger PH. Infantile haemangioma. *Lancet* 2017; 390(10089): 85–94.
3. Vivar KL, Mancini AJ. Infantile Hemangiomas: An Update on Pathogenesis, Associations, and Management. *Indian J Paediatr Dermatology* 2018; 19: 293–303.
4. MacArthur KM, Püttgen K. Vascular Tumors. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., editors. *Fitzpatrick's Dermatology 9th Edition*. New York: McGraw-Hill Education; 2019. p. 2042–65.
5. Grzesik P, Wu JK. Current perspectives on the optimal management of infantile hemangioma. *Med Ther* 2017;(8): 107.
6. Lydiawati E, Zulkarnain I. Infantile Hemangioma: A Retrospective Study. *Berkala Ilmu Kesehatan Kulit dan Kelamin* 2020; 32(1): 21.
7. Chen ZY, Wang QN, Zhu YH, Zhou LY, Xu T, He ZY, et al. Progress in the treatment of infantile hemangioma. *Ann Transl Med* 2019; 7(22): 692–692.
8. Harter N, Mancini AJ. Diagnosis and Management of Infantile Hemangiomas in the Neonate. *Pediatr Clin North Am* 2019; 66(2): 437–59.
9. Saoji R, Shirolkar M. Successful use of propranolol in infantile hemangiomas. *Indian J Drugs Dermatol* 2017; 3: 77–80.
10. El Hachem M, Gesualdo F, Diociaiuti A, Berti I, Vercellino N, Boccaletti V, et al. Safety and effectiveness of oral propranolol for infantile hemangiomas started before 5 weeks and after 5 months of age: An Italian multicenter experience. *Ital J Pediatr* 2017; 43(1): 4–9.
11. Tamez HM, Sobel R. Review of the treatment of periocular infantile hemangiomas with beta blockers. *Int Ophthalmol Clin* 2017; 57(1): 169–76.
12. Sun LM, Xu Y, Xu MN, Wang M, Su Y, Yuan SM. Diagnosis and treatment of periorbital infantile hemangiomas: Case series and literature review. *Int J Pediatr Otorhinolaryngol* 2020; 136: 110157.
13. Samuelov L, Kinori M, Rychlik K, Konanur M, Chamlin SL, Rahmani B, et al. Risk factors for ocular complications in periocular infantile hemangiomas. *Pediatr Dermatol* 2018; 35(4): 458–62.
14. Tavakoli M, Yadegari S, Mosallaei M, Aletaha M, Salour H, Lee WW. Infantile Periocular Hemangioma. *J Ophthalmic Vis Res* 2017;(2): 205–201.
15. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, Blei F, Greene AK, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. *Pediatrics* 2019; 143(1).
16. Al-Haddad C, El Salloukh NA, El Moussawi Z. B-Blockers in the Treatment of Periocular Infantile Hemangioma. *Curr Opin Ophthalmol* 2019; 30(5): 319–25.
17. Püttgen KB. Diagnosis and Management of Infantile Hemangiomas. *Pediatr Clin North Am* 2014; 61(2): 383–402.

18. PERDOSKI. Hemangioma Infantil. In: Panduan Praktik Klinis Bagi Dokter Spesialis Kulit dan Kelamin di Indonesia. Jakarta. 2017. p. 324–7.
19. Yarbrough KB, Tollefson MM, Krol AL, Leitenberger SL, Mann JA, MacArthur CJ. Is Routine Electrocardiography Necessary Before Initiation of Propranolol for Treatment of Infantile Hemangiomas? *Pediatr Dermatol* 2016; 33(6): 615–20.
20. Shah MK, Vasani RJV. Use of Propranolol in Infantile Hemangioma. *Indian J Drugs Dermatol* 2017; 3: 48–52.