Successful Use of Propranolol in Infantile Hemangiomas

Rajendra Saoji, Manasi Shirolkar

Consultant Paediatric Surgeon, Midas Heights, Ramdaspeth, Department of Dermatology, NKP Salve Institute of Medical Sciences, Lata Mangeshkar Hospital, Nagpur, Maharashtra, India

Abstract

Infantile hemangioma (IH) is a benign vascular tumor of the capillary endothelium that exhibits a characteristic clinical course of early rapid growth followed by spontaneous slow involution by the first decade of life. Most IHs regress spontaneously by the end of the 1st year, but some may require urgent medical or surgical intervention if they encroach on vital organs affecting their function; or may cause significant cosmetic disfigurement on the resolution. We report three cases of large IHs over eyelid, vulva, and the tongue which were causing considerable impairment or were cosmetically disfiguring and in whom surgery was difficult due to their anatomic location. In these cases, oral propranolol therapy was initiated with successful outcomes. Propranolol was well tolerated in all these patients without significant side effects.

Keywords: Infancy, Infantile hemangioma, propranolol

INTRODUCTION

Hemangiomas are benign tumors of the endothelium of blood vessels in infants. The incidence ranges from 1% in neonates to 12% at 1 year[1‑5] seen more often in premature newborns and infants who have had chorionic villus sampling.[6] Hemangiomas undergo 3 phases, i.e., proliferative phase showing postnatal growth for 8–12 months; involuting phase over the next 1–5 years consisting of regression and phase of involution showing continuous improvement until 6–12 years. Complications such as ulceration, vital structure compression, and visceral involvement may be seen depending on size and location of hemangioma.[7‑10] Facial hemangiomas may cause disfigurement and scarring.[3,7,8]

Current medical therapeutic modalities for complicated hemangiomas include topical, intralesional and systemic steroids, recombinant interferons alpha‑2a and 2b, vincristine, imiquimod, etc. Interventional therapies include cryotherapy, Argon, Nd‑YAG, flashlamp‑pumped pulse dye laser, embolization, sclerotherapy, surgery, and radiotherapy.[3,4,6‑13] The mainstay of treatment continues to be “wait‑and‑watch.” Here, we describe 3 cases of hemangioma treated with propranolol.

CASE REPORTS

Case 1

A 2-year-old female child came with reddish lesion on the right side of face since birth [Figure 1a]. There was rapid increase in size to the current state where it had formed a large vascular nodule. The child had not received any treatment earlier. The lesion was not posttraumatic or associated with tenderness, discharge. General and systemic examination was normal. On cutaneous examination, there were soft compressible reddish nodules present over the right eyelid and eyebrow and extending onto the temporal area and lateral side of forehead, suggestive of hemangioma. There was associated narrowing of the right palpebral fissure because of the size of hemangioma leading to decreased vision. Due to the localization of the hemangioma over the right eyelid, there was imminent danger of amblyopia. As the site of hemangioma was difficult for surgical excision, we decided to start this patient on oral propranolol. The patient was treated over the course of 3 years intermittently with oral propranolol at the dose of 1 mg/kg/day for 3 days under supervision, with close monitoring of hypotension, bradycardia (by pulse oximeter), and hypoglycemia (by glucometer). Imaging was done in the form of two‑dimensional (2D)‑echo, which was normal. As there were no adverse effects noted, the dose was stepped up to 2 mg/kg/day. The patient tolerated the treatment well. There was rapid response within a week with regards to alteration...
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in color and texture. At the end of 3 months [Figure 1b], significant improvement was noted, which continued till next 6 months [Figure 1c]. There was near total clearance of hemangioma at the end of 5 years [Figure 1d].

**Case 2**

A 3-month-old female child presented with lesions on genitals since first 2 weeks of life [Figure 2a]. The child had not received any treatment beforehand. The lesion was not posttraumatic or associated with tenderness, discharge. General and systemic examination was normal. On cutaneous examination, there was soft compressible vascular swelling over the right side of labia major extending to right perianal region, suggestive of hemangioma. The site was not amenable to surgery due to its anatomical location. The patient was treated with oral propranolol at the dose of 1 mg/kg/day for 3 days under supervision, with close monitoring of hypotension, bradycardia (by pulse oximeter), and hypoglycemia (by glucometer). Imaging was done in the form of 2D-echo, which was normal. As there were no adverse effects noted, the dose was stepped up to 2 mg/kg/day and was given for 12 months. The patient tolerated the treatment well. Over the course of one year [Figures 2a-d], the lesion completely regressed with almost no scarring, with response being noted as early as 7 days.

**Case 3**

An 8-year-old female child came with lesions on dorsal and ventral surfaces of the tongue since first 2 weeks of life [Figure 3a and b]. The lesions were associated with recurrent bleeding, not associated with pain or trauma. The general and systemic examination was normal. Cutaneous examination revealed multiple bluish-red vascular lesions on the tongue. As this site was difficult for surgical excision, we decided to start this patient on oral propranolol. The patient was given oral propranolol at 1 mg/kg/day for 3 days under supervision, with close monitoring of hypotension, bradycardia (by pulse oximeter), and hypoglycemia (by glucometer). Imaging was done in the form of 2D-echo, which was normal. As there were no adverse effects noted, the dose was stepped up to 2 mg/kg/day and was given for 12 months. The patient tolerated the treatment well. Over the course of one year [Figures 3c and d], the lesion completely regressed with almost no scarring, with response being noted within a week in the form of change in size and texture. There was no recurrence of hemangioma after discontinuation of propranolol.

**DISCUSSION**

Propranolol, is a nonselective beta-blocker and if not contraindicated, stands as the first-line agent for hemangiomas that impair function or cause permanent disfigurement.[14] In 2014, propranolol hydrochloride oral solution was approved by the US Food and Drug Administration for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy.[15] Other modalities of treatment for IHs include oral steroids, vincristine, interferon alpha, surgery, and pulsed dye laser, but these are cumbersome and associated with variable side effects and complications. Surgical excision at times is not possible due to difficult anatomic sites and due to risk of cosmetic disfigurement.

The efficacy of propranolol in IHs was reported serendipitously by Léauté-Labrèze et al. in 2008 where the use of propranolol in their patient for hypertrophic cardiomyopathy caused by corticosteroids lead to dramatic improvement in patient’s hemangioma.[16] Propranolol inhibits the growth and induces regression of IHs by its potential mechanisms of inducing vasoconstriction, decreased expression of vascular endothelial growth factor and matrix metalloproteinases, and/or triggering of apoptosis.[16-18] The proposed mechanism of action of propranolol in hemangiomas included vasoconstriction, apoptosis of capillary endothelial cells,[19] and decreased the production of vascular endothelial growth factor and fibroblastic growth factor. During the growth phase, these latter two major pro-angiogenic factors are involved. Propranolol...
leads to decreased expression of genes related to them and
down-regulation of the rapidly accelerated fibrosarcoma
mitogen-activated protein kinase pathway\cite{19} and the triggering
of apoptosis of capillary endothelial cells.\cite{20}

Since then, due to its effects on vascular endothelium, it has
been used to treat hemangiomas by many others and was found
to be safe.\cite{21} In rare instances, the drug has been reported to
cause adverse effects such as hypoglycemia, bradycardia,
hypotension, bronchospasm,\cite{22} and high output cardiac failure
in infants with very large hemangiomas. All our patients,
however, showed no adverse effects, with dramatic regression
of hemangioma clinically.

One must be careful using propranolol in cases of posterior
fossa malformations, hemangiomas, arterial abnormalities,
cardiac defects, eye abnormalities, sternal cleft, and
supraumbilical raphe syndrome (PHACES syndrome) since
potentially hypoperfusion of the brain is a small possibility.

Contraindications to the use of propranolol are reported to be
cardiogenic shock, documented chronic and significant sinus
bradycardia, documented chronic and significant hypotension,
greater than first-degree heart block, heart failure, history of
bronchospasm or wheezing, hypersensitivity to propranolol,
and preterm infants with corrected age <5 weeks (postnatal
age in weeks − number of weeks preterm). Our patients
did not have any of these conditions and hence was administrated
oral propranolol for a long duration of time.

As per conventional literature, the pretreatment evaluation
should include detail history to rule out cardiovascular
and respiratory abnormalities (e.g., poor feeding, dyspnea,
tachypnea, diaphoresis, wheezing, heart murmur, and family
history of heart block or arrhythmia). The thorough physical
examination should be performed for cardiac or pulmonary
assessment and measurement of heart rate and blood pressure.

Imaging studies including cardiac ultrasound or cardiac magnetic
resonance imaging should be obtained in children with large
facial hemangiomas at risk for PHACES to rule out the possibility
of severe aortic coarctation, which is a contraindication for
propranolol use. In these patients, baseline head and neck MRI
with angiography are also preferred before propranolol unless
the clinical situation requires urgent treatment (e.g., severe
visual obstruction due to an orbital hemangioma). In such cases,
propranolol can be initiated at a lower dose and slowly titrated up
to a maximum dose of 1 mg/kg/day.\cite{23} However, we could not
perform these investigations due to lack of facilities.

**Conclusion**

Many treatment modalities are available to treat IHs. Of these,
propranolol seems to be the most promising. However, more
studies are needed to confirm the efficacy of propranolol before
considering it as a possible first-line drug in the treatment of
infantile hemangiomas.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate
patient consent forms. In the form the patient(s) has/have
given his/her/their consent for his/her/their images and other
clinical information to be reported in the journal. The patients
understand that their names and initials will not be published
and due efforts will be made to conceal their identity, but
anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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