Excellent response of infantile orofacio-orbital hemangioma to propranolol-pictorial depiction and literature review

Jonathan Theodore Gondi, Suhasini Gazula[1], A. Rajasekhar[1], G. Usharani[1]

Abstract

Infantile hemangiomas (IHs) are common, benign vascular tumors of infancy, with more than half affecting the head and neck region. IHs involving the lips and oral cavity can often present to the oral surgeon and the pedodontist. Till date, several doubts exist among clinicians regarding the use of propranolol to treat infantile hemangiomas in neonates and small infants, appropriate dose, treatment duration, side effects, response, and long-term follow-up. We present a 2-month-old male infant with extensive hemangioma involving the face, orbit, buccal mucosa and palate with feeding difficulties, and risk of life-threatening complications such as airway compromise, aspiration, and visual loss which showed excellent response with high-dose propranolol and had no side effects. We also reviewed literature for the mechanism of action of propranolol and possible minor and serious side effects.

Keywords: Hemangioma, infant, orbital, orofacial, propranolol

Introduction

Infantile hemangiomas (IHs) are common, benign vascular tumors of infancy, 50–60% of which affect the head and neck area.[1] Although usually innocuous and self-limiting, they can cause serious complications such as airway compromise, visual loss, severe anemia, and high-output cardiac failure. Till recently, treatment modalities included steroids, bleomycin, vincristine, etc. Léauté-Labrèze *et al*. reported the effect of propranolol in IHs, which provoked a paradigm shift in its management.[2] However, important questions remain unanswered, and doubts exist among clinicians regarding use in neonates and small infants, optimal dose, duration of treatment, monitoring for side effects, resolution rate, and long-term follow-up.

We present a 2-month-old male infant with extensive hemangioma, involving the face, orbit, buccal mucosa, and palate with potential life-threatening complications of airway compromise, aspiration of blood, and loss of vision which we treated with high-dose propranolol under the strict monitoring and had rapid, excellent response with no side effects.

Case Report

A 2-month-old male infant presented with the complaints of red patch over the entire right side of the face and right side of the palate. The lesion was small at birth but rapidly increased in size. The baby was unable to open the right eye due to the involvement of the right upper eyelid and had difficult in breastfeeding due to the involvement of the upper lip. There were no other lesions elsewhere on the body and no associated symptoms of bleeding, airway compromise, or cardiovascular complications.

Examination revealed a large 10 cm × 12 cm bright red hemangioma involving the right hemiface, including the right orbit, the right half of upper lip, [Figure 1] and extending intraorally to involve the right buccal mucosa, the right half of uvula and mucosa of right half of hard, and soft palate. Lesion blanched on pressure, was nonpulsatile and no bruit was heard on auscultation. Detailed eye examination (visual acuity, anterior chamber, fundus, etc.,) was done by the pediatric ophthalmologist and was normal.

Department of Head and Neck Oncology, Basavatarakam Indo American Cancer Hospital and Research Institute, [1]Department of Pediatric Surgery, Employees State Insurance Corporation, Super Speciality Hospital, Hyderabad, Telangana, India

Correspondence: Dr. Suhasini Gazula,
Department of Pediatric Surgery, Employees State Insurance Corporation, Super Speciality Hospital, Sanathnagar, Hyderabad - 500 038, Telangana, India.
E-mail: suhasinigazula@gmail.com

Access this article online	
Quick Response Code:	Website: www.contempclindent.org
	DOI: 10.4103/0976-237X.183060

How to cite this article: Gondi JT, Gazula S, Rajasekhar A, Usharani G. Excellent response of infantile orofacio-orbital hemangioma to propranolol-pictorial depiction and literature review. Contemp Clin Dent 2016;7:269-72.

Blood investigations were normal. Magnetic resonance imaging showed a T1-iso, T2-hyperintense 15 mm × 15 mm × 15 mm lesion in the extraconal, and conal space of the right orbit with postcontrast intense homogenous enhancement suggestive of low-flow vascular malformation. Magnetic resonance-angiogram showed prominent branches of the right middle meningeal and lacrimal branches of the right ophthalmic arteries [Figure 2].

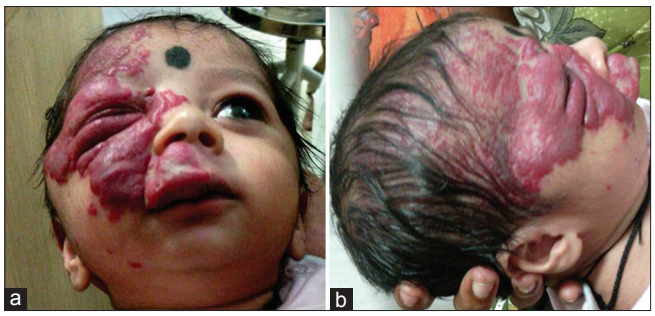

Figure 1: (a and b) Large, bright red hemangioma involving the right hemiface, including the right frontotemporal region, right orbit, right cheek, and right half of the upper lip

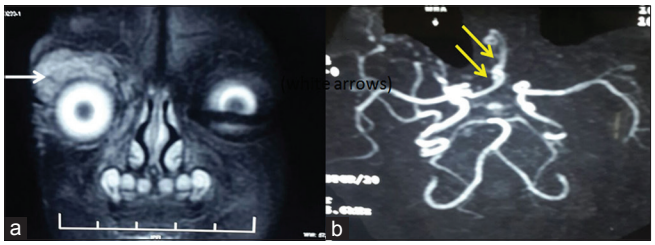

Figure 2: (a) Magnetic resonance imaging showing T1-iso, T2-hyperintense 15 mm × 15 mm × 15 mm lesion (white arrow) in extraconal and conal space of right orbit (b) magnetic resonance-angiogram showing prominent branches of the right middle meningeal and right ophthalmic arteries (yellow arrows)

Oral propranolol was planned after explaining risks and benefits to the parents. Pretreatment evaluation involved a thorough personal and familial history for atopy, asthma, recurrent wheezing, and elaborate clinical examination for multiple hemangiomas, electrocardiography, blood pressure, and blood glucose levels. An echocardiogram was done by pediatric cardiologist which was normal.

After hospital admission, propranolol was initiated at 2 mg/kg - body-weight/day as a single oral dose with hourly monitoring of heart rate, respiratory rate, and blood pressure. To avoid the potential side effect of hypoglycemia with propranolol, it was administered soon after feeding, and blood glucose was measured after 4 h of the first dose and then 12th hourly for 2 days. No side effects were noted. Rapid response was observed within 48 h evident by the immediate cessation of growth, softening, and fading of erythema [Figure 3]. Baby was discharged after 48 h with detailed instructions regarding dose, administration after feeds, warning signs (wheeze, lethargy, etc.,), and to bring the child immediately if any of the signs noted.

The baby was followed up in the outpatient clinic for the 1st month on a 2-weekly basis, then onward at a monthly interval. Significant response was noted at 2 weeks with paleness of the lesion and disappearance of about 25% of the oral lesions. The baby was also able to open the right eye and even feed easily. By 2nd month, oral (palatal and buccal) lesions completely disappeared with no residual scar while the facial and orbital lesions decreased more than 30%. At 4-month follow-up, there was 50% resolution and at 7-month, there was complete disappearance of the orbital hemangioma and normal eye movements. At 8.5 months, there is near-total (~95%) resolution with 100% parental satisfaction, excellent

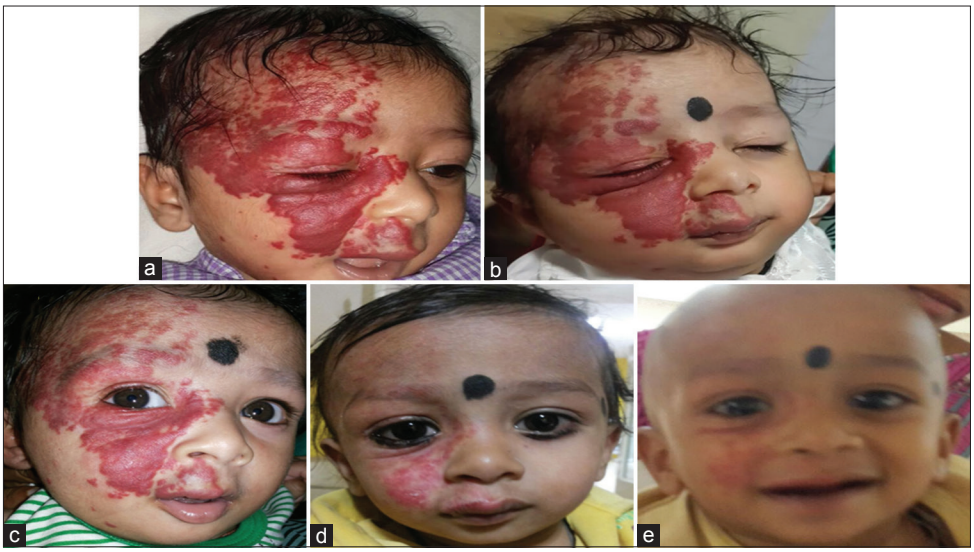

Figure 3: (a) Response at 48 h evident by cessation of growth, softening, and fading of erythema (b) 2 weeks: Paleness of lesion and decrease in bulkiness of right upper eyelid (c) 2 months: Facial and orbital lesions decreased more than 30% and able to open right eye with ease (d) 7 months: Complete disappearance of the orbital hemangioma and normal eye movements (e) 8.5 months: Near-total (~95%) resolution with excellent cosmesis and no residual scarring

cosmesis, and no residual scarring [Figure 3]. Baby had no side effects and maintained normal respiratory and cardiovascular parameters.

Gradual tapering and stoppage of propranolol is planned over next 2 months with continued monthly surveillance for 6 more months for any relapse.

Discussion

Infantile capillary hemangiomas are benign vascular tumors with typical clinical course, characterized by rapid proliferative phase in early infancy, followed by an involutional phase. Female:male ratio is 3:1–5:1 with higher incidence in prematurity, low birth-weight, placentary anomalies and multiple pregnancies.[1]

IHs present as small tumors at birth or first 2–3 months too, proliferate during 1st year (most prominent growth during first 4–6 months), and involute over 5–7 years. As a thumb-rule, 50% of IHs involute by 5 years, 70% by 7 years of age, and remaining may take 3–5 years more. Even after involution, permanent residues may present as scars, telangiectasia, or redundant skin.[3]

While most are innocuous and spontaneously resolving, some IHs can cause major complications such as airway compromise, serious visual loss through induction of strabismic, deprivational, or anisometropic astigmatism, severe anemia, Kasabach–Meritt syndrome, and high-output cardiac failure.[4,5] Feeding difficulties due to oral hemangiomas can lead to poor sucking as was noted in our patient or bleeding during sucking resulting in malnutrition and anemia in infants causing extreme parental anxiety.

Various pharmacological agents such as steroids (systemic or intralesional), interferon, vincristine, bleomycin, cyclophosphamide, or imiquimod have been used in the treatment of IH with no single uniformly safe and effective treatment.[6] The report about the impressive effect of propranolol in treating IHs provoked a paradigm shift in their management with several reports since then. However, little is known on the exact mechanism of propranolol. One explanation is the induction of vasoconstriction, which is immediately visible as a change in color, and palpable softening of the hemangioma.[2] Beta-blockers could also influence signal-transduction-pathway of angiogenic factors (basic fibroblast-growth-factor, vascular-endothelial-growth-factor,[7] thereby effecting the proliferative phase. Propranolol's ability to trigger apoptosis in capillary endothelial cells in rat lung tissue[8] might also be applicable to hemangioma endothelial cells.

In a large systematic review of IHs treated with propranolol, Marqueling *et al*. reported the most common adverse events as changes in sleep and acrocyanosis seen in 11.4% and 5.1% patients and rare incidence of serious adverse events such as symptomatic hypotension in 0.4%, hypoglycemia in 0.3%, and symptomatic bradycardia in 0.08% patients, respectively.[9] Likewise, restless sleep, constipation, and cold extremities were also observed by de Graaf *et al*. but they concluded that side effects such as symptomatic hypoglycemia, hypotension, and bronchial hyperreactivity that needed intervention and/or close monitoring were infrequent and not dose-dependent.[10] Xu *et al*. noted that fluctuations from the normal range of cardiovascular parameters occurred frequently with initiating propranolol, but were clinically asymptomatic.[11] Similarly, our patient also did not develop any major or minor side effects despite initiating a relatively higher dose of propranolol. It has also been suggested quite wisely that as propranolol may blunt clinical features of hypoglycemia, it should be avoided in neonates in their 1st week of life when symptomatic hypoglycemia is more likely to develop.[12] Broeks *et al*. reviewed IHs of the airway and concluded that while propranolol was effective in 90% of the cases, 8.6% patients were classified as nonresponders. Nearly 9.8% patients relapsed while weaning of propranolol or after discontinuation, and 1.2% cases appeared resistant to re-initiation of therapy.[5]

Despite several reports since 2008,[4,5,9-11] even now several doubts exist among clinicians regarding use in neonates and small infants, dosing and duration, monitoring for side effects, and parental counseling. Further research should focus on the optimal treatment protocol, optimal dose range, duration of treatment, resolution rate, predictors of relapse, long-term follow-up, and the actual percentage of nonresponders. The mechanism of resistance to propranolol is also unknown and needs to be illuminated.

Conclusion

Propranolol seems to be a rapidly effective and safe treatment strategy for complex IH. Nevertheless, only a minority of patients with life-threatening situations or severe functional impairment require active medical intervention. Administering systemic medication to an infant with a benign condition requires careful consideration and should be advised only by experienced clinicians trained in handling neonates and infants. Side effects may be noted, but serious adverse effects are rare. Close monitoring of the babies is required, considering the risk of serious side effects, relapse, and resistance to propranolol.

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Hemangioma Investigator Group, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, *et al.* Prospective study of infantile hemangiomas: Demographic, prenatal, and perinatal characteristics. J Pediatr 2007;150:291-4.
2. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649-51.
3. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: Clinical application of a new classification. J Pediatr Surg 1983;18:894-900.
4. Claerhout I, Buijsrogge M, Delbeke P, Walraedt S, De Schepper S, De Moerloose B, *et al.* The use of propranolol in the treatment of periocular infantile haemangiomas: A review. Br J Ophthalmol 2011;95:1199-202.
5. Broeks IJ, Hermans DJ, Dassel AC, van der Vleuten CJ, van Beynum IM. Propranolol treatment in life-threatening airway hemangiomas: A case series and review of literature. Int J Pediatr Otorhinolaryngol 2013;77:1791-800.
6. Nguyen J, Fay A. Pharmacologic therapy for periocular infantile hemangiomas: A review of the literature. Semin Ophthalmol 2009;24:178-84.
7. Iaccarino G, Ciccarelli M, Sorriento D, Galasso G, Campanile A, Santulli G, *et al.* Ischemic neoangiogenesis enhanced by beta2-adrenergic receptor overexpression: A novel role for the endothelial adrenergic system. Circ Res 2005;97:1182-9.
8. Sommers Smith SK, Smith DM. Beta blockade induces apoptosis in cultured capillary endothelial cells. *In Vitro* Cell Dev Biol Anim 2002;38:298-304.
9. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: A systematic review. Pediatr Dermatol 2013;30:182-91.
10. de Graaf M, Breur JM, Raphaël MF, Vos M, Breugem CC, Pasmans SG. Adverse effects of propranolol when used in the treatment of hemangiomas: A case series of 28 infants. J Am Acad Dermatol 2011;65:320-7.
11. Xu DP, Cao RY, Xue L, Sun NN, Tong S, Wang XK. Treatment of severe infantile hemangiomas with propranolol: An evaluation of the efficacy and effects of cardiovascular parameters in 25 consecutive patients. J Oral Maxillofac Surg 2015;73:430-6.
12. Love JN, Sikka N. Are 1-2 tablets dangerous? Beta-blocker exposure in toddlers. J Emerg Med 2004;26:309-14.