Beta-Blockers as Therapy for Infantile Hemangiomas

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Abstract

Keywords

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Infantile hemangiomas (IH) are common benign vascular tumors seen in children. Although the majority will improve spontaneously without treatment, a small subset will require therapy due to a variety of complications. Less than a decade ago, propranolol replaced corticosteroids as first-line treatment for most IH and it has proven to be a relatively safe, effective therapy. After initiation of propranolol, most hemangiomas show evidence of significant improvement relatively rapidly, often within days. Although propranolol is generally felt to have a more limited side-effect profile than systemic corticosteroids, its use has been infrequently associated with adverse events, including sleep disturbances, acrocyanosis, hypotension, bradycardia, respiratory events, and hypoglycemia. Rarely, hypoglycemic seizures have been reported, usually occurring in the setting of prolonged fasting.

Infantile hemangiomas (IHs), the most common tumor of childhood, are benign proliferations of vascular endothelium. Though often not evident at the time of birth, superficial hemangiomas usually appear on the skin within the first month of life as bright red papules or plaques. Deep hemangiomas may take longer to develop and often appear as skin-colored to bluish subcutaneous swellings. Although many IH will not cause significant problems, a small subset will result in complications such as ulceration, bleeding, functional impairment, or permanent cosmetic deformity.^{1,2} Rarely, hemangiomas may be associated with life-threatening complications, such as severe bleeding, respiratory compromise, congestive heart failure, or liver failure.³ Estimated to affect up to 4% to 5% of Caucasian infants, they have been reported in familial clusters with an autosomal dominant pattern; however, the vast majority of cases occur sporadically.^{4,5} Known risk factors include low birth weight, Caucasian ethnicity, female gender, advanced maternal age, and a variety of prenatal complications (including placenta previa and pre-eclampsia).⁶

Infantile hemangiomas are typically characterized by rapid growth during the first weeks to months of life, followed by

a variable plateau and an involution phase in which spontaneous regression occurs over a period of months to years.⁷ In most cases, a diagnosis can be made clinically, based on the appearance of the lesion, as well as the timing of its appearance and its overall growth pattern. Histologic examination during the proliferative phase reveals superficial proliferating endothelial cells with few capillary lumina.⁸ The involution phase is characterized by fibrosis of capillary lumina.

The exact pathogenesis of IH is incompletely understood, though markers not expressed in normal dermal or subcutaneous tissues are frequently detected in IH. In particular, vascular endothelial growth factor (VEGF), glucose transporter-1 (GLUT-1), and placenta-associated vascular antigens (i.e., Fc γ RII, merosin, and Lewis Y antigen) are highly expressed in the endothelial cells of IH throughout both the rapid growth phase and the involution phase.⁹ Interestingly, the only other vascular tissue known to share a similar expression profile is from placental chorionic villi. Some current experimental evidence proposes that IH may derive from clonal proliferations of endothelial cells through the de novo formation of primitive blood vessels from angioblasts.^{10,11} At some point, typically by the second year of life, unknown triggers halt the

proliferation and increase the rate of apoptosis, marking the transition into the involution phase.¹² Increased numbers of mast cells and levels of tissue metalloproteinase (an inhibitor of new blood vessel formation), upregulation of interferon-induced genes, and decreased quantities of fibroblast growth factor (FGF) have been identified as potential molecular mediators of IH involution.^{13–15}

The mainstay of therapy for IH is active nonintervention (i.e., watchful waiting) as most lesions are uncomplicated and will involute spontaneously without significant sequelae.¹⁶ However, intervention is often required for a clinically significant subset of IH that are causing severe organ dysfunction (such as congestive heart failure or liver failure), functional impairment (such as impairment of vision, feeding, or breathing), or significant cosmetic deformity (such as large facial, nasal tip, lip, breast, and genital lesions).⁷ For many years, the first-line medical treatment for complicated lesions was corticosteroids, including topical, intralesional, and systemic approaches. Unfortunately, corticosteroids were inconsistent in efficacy and systemic treatment was fraught with adverse side effects, including the development of Cushingoid features, gastroesophageal reflux, hypertension, growth retardation, and increased susceptibility to infection.¹⁷ However, a major breakthrough occurred in 2008 when Leaute-Labreze et al observed that a group of children with IH who received therapy with the nonselective beta-blocker propranolol experienced marked improvement in their lesions.¹⁸ Since this serendipitous discovery, many studies have been published demonstrating the efficacy and safety of propranolol as first-line therapy for problematic hemangiomas of infancy. Here, we describe the emergence of the use of β -blockers for the treatment of IH and highlight the current guidelines for their use in managing this condition.

Discovering a New Indication for β -Blockers

In a landmark research letter, Leaute-Labreze and coauthors reported stabilization in IH growth following administration of propranolol.¹⁸ The authors initially noted that two children with facial IH who received propranolol for cardiac conditions experienced significant visible improvement in their hemangiomas. They then followed this report with a study in which 32 children with IH (mean age at onset of treatment was 4.8 months) received 2 to 3 mg/kg/d of propranolol, delivered in two or three divided doses.¹⁹ Immediate improvement was observed in all cases and was especially notable in cases where IHs were causing hemodynamic compromise or palpebral occlusion. These findings triggered a cascade of subsequent studies, collectively demonstrating the overall superiority of propranolol for medical therapy of problematic IH.²⁰

Clinically, administration of propranolol typically induces significant softening and improvement in color of hemangiomas, often within the first few hours or days after initiating therapy.³ Compared with corticosteroids, propranolol appears to be more rapid and effective in its treatment response. In a randomized trial, 30 children aged 1 to 8 months with potentially disfiguring or functionally threatening hemangiomas were treated with oral propranolol (2–3 mg/kg/d), oral

prednisolone (1–4 mg/kg/d), or a combination of both drugs. The mean response time was shorter in children receiving propranolol with or without prednisolone than in those receiving prednisolone alone (4.1 and 4.7 days, respectively, vs. 9.8 days).²¹ Moreover, the side effects reported by the prednisolone group during treatment were unfavorable when compared with those reported in the propranolol group, which consisted of one asymptomatic episode of hypoglycemia and somnolence. A 2012 meta-analysis also found response rates to β -blockers to be superior, reporting 69% versus 97% ($p < 0.001$) for corticosteroids and propranolol, respectively.³ Several subsequent studies have reported similar observations, supporting the significant efficacy of β -blockers in the treatment of IH.

The exact mechanism of action of β -blockers for the treatment of IH has not been completely elucidated, although it is believed to inhibit tumor growth by at least three distinct mechanisms: (1) vasoconstriction; (2) inhibition of angiogenesis or vasculogenesis by downregulation of angiogenic factors, VEGF, and basic FGF; and (3) induction of apoptosis of capillary endothelial cells.³ These mechanisms correspond, respectively, with fading of color, cessation of growth, and long-term regression.²²

Side Effects and Rebound Growth

Propranolol has long been used in children for a variety of conditions, including supraventricular tachycardia, neonatal hyperthyroidism, and arrhythmias, and is generally considered to have a good safety profile. A systematic review identified 371 adverse events in 1,189 children treated with propranolol for hemangiomas.²³ The most common adverse events included sleep disturbance (136 patients), acrocyanosis (61 patients), hypotension (39 patients), bradycardia (8 patients), and respiratory events including infections, stridor, and wheezing (35 patients). Notably, only five patients with hypotension and one patient with bradycardia were symptomatic. Certainly, the most alarming potential problem associated with propranolol treatment is symptomatic hypoglycemia (four patients), which resulted in hypoglycemic seizures in one child.²⁴ Hypoglycemia is thought to result from blockade of β -receptors, leading to inhibition of glycogenolysis, gluconeogenesis, and lipolysis. Children on propranolol therapy appear to be at increased risk for hypoglycemic complications during periods of prolonged fasting or poor oral intake. As a result, it is imperative that caregivers are counseled about this potential adverse event. Strategies to avoid hypoglycemia include scheduled feedings and administration of medication following feeds.

Several articles have reported rebound growth, or recurrence of IH, following discontinuation of propranolol. The same systematic review identified a rate of 17% for rebound growth, and a recent study observed rebound growth in 5 out of 26 patients (19%).^{23,25} Time from cessation of treatment to recurrence ranged from 0 to 6 months. Although predictive factors for recurrence are still unidentified, rebound growth is believed to be related to early treatment withdrawal or a prolonged proliferative phase of IH.³

Clinical Guidelines

Although β -blockers are not currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of IH, the consistently positive results from published studies to date have led to clinical guidelines for initiating and monitoring propranolol treatment in select patient populations.²⁶

Pretreatment evaluation of patients should include a thorough physical examination with particular focus on cardiovascular and respiratory abnormalities. Family history of heart block or arrhythmia should also be ascertained. In children with bradycardia, history of arrhythmia or cardiovascular abnormality on physical exam, or in patients with family history of congenital heart disease, an electrocardiogram (ECG) should be included in the pretreatment workup.²⁶

It is suggested that hospitalization for initiation of propranolol be strongly considered for infants younger than 2 months of age, patients with medical comorbidities relating to the cardiovascular or respiratory system, and patients of any age with conditions affecting blood glucose homeostasis. For otherwise healthy infants over 2 months of age, propranolol may be initiated in an outpatient setting, unless the clinician suspects inadequate social support.²⁶ Initial dosing of propranolol starts at 0.5mg/kg/d in three divided doses. The dose is then escalated slowly to a maximum of 2 mg/kg/d in three divided doses. The pharmacokinetics of oral propranolol are characterized by a peak effect 1 to 3 hours after admission; therefore, it is recommended that heart rate and blood pressure be monitored 1 to 2 hours after the initial dose. It is also recommended that vital signs are obtained after dose increases greater than 0.5 mg/kg/d, as well as after the target dose has been reached.²⁶

Given that many patients will undergo outpatient treatment, it is important that clinicians educate parents about recognizing signs of hypotension, bradycardia, and hypoglycemia. Early signs of hypoglycemia include sweating, shakiness, tachycardia, anxiety, and hunger, all of which may be masked by β -blockers with the important exception of sweating. Because sweat glands are innervated by cholinergic nerve terminals, sweating may be the most reliable early sign of hypoglycemia and should be emphasized to caregivers. Currently, experts do not recommend routine screening of serum glucose in otherwise healthy infants.

Other β -Blockers

The mechanism of nonselective β -blocking is responsible for the adverse effects associated with propranolol use. Therefore, more selective systemic β -blockers—such as atenolol, nadolol, and acebutolol—have been explored as potential alternatives for treating IH.^{27–29} Atenolol, a hydrophilic β_1 -blocker, was successfully used to treat two children who had to discontinue propranolol due to adverse effects.²⁷ Interestingly, the treatment response was slower than that observed with propranolol therapy, and the immediate fading of hemangioma color was not seen with atenolol, suggesting that this improvement may be mediated by β_2 -specific blocking. Similarly, due to concerns about potential long-term

effects of β -adrenergic inhibition on higher-level brain function, a 2013 study examined the use of the nonselective agent nadolol for its inability to cross the blood–brain barrier.²⁸ Nadolol also has a longer half-life than propranolol, requiring less frequent dosing. This cohort study of 10 children treated with nadolol over 6 months resulted in complete involution of all hemangiomas.²⁸ Comparable results have been reported for acebutolol in the treatment of subglottic hemangiomas.²⁹

For superficial or small IH, in which systemic β -blocker therapy may not be indicated, topical β -blockers, specifically timolol gel-forming solution (GFS), have proven to be a useful alternative.³⁰ Some studies also suggest a potential role of topical β -blockers in preventing rebound growth in children who are being tapered off oral propranolol. If a decision is made to use topical β -blockers, many experts suggest that timolol 0.5% GFS may be used twice per day. In a recent multicenter retrospective study examining the efficacy of timolol 0.1% or 0.5% GFS applied twice daily for superficial IH, 72 of 73 patients exhibited some improvement, with the mean duration of therapy being 3.4 months.³⁰ Although the efficacy of topical timolol has been confirmed in several case series thus far, there are some concerns about potential side effects of this medication. Its marked potency over propranolol and bypass of first-pass liver metabolism warrant that clinicians continue to exercise caution until further information about the pharmacokinetic profile of topical timolol becomes available. To date, a small amount of topical timolol appears to be safe, although the exact levels of systemic absorption are difficult to quantify. For this reason, most clinicians avoid using topical timolol on ulcerated and mucosal lesions.

Conclusion

Propranolol has rapidly replaced systemic corticosteroids as first-line therapy for complicated hemangiomas of infancy. Although its side-effect profile is overall favorable compared with that for corticosteroids, patients must be monitored closely for rare, but potentially serious, adverse events. Caregivers should be mindful of regular feeding intervals and alert to abnormal sweating, perhaps the most reliable indication of hypoglycemia during propranolol treatment. The adverse effects associated with the nonselective β -blockade of propranolol have prompted the investigation of other β -blocking agents for the treatment of IH. Early studies have yielded promising results, but further research is necessary to clarify whether these alternatives match or exceed propranolol's efficacy and side-effect profile. For now, propranolol remains the mainstay of treatment for most children with complicated IH.

References

- 1 Bruckner AL, Frieden IJ. Hemangiomas of infancy. *J Am Acad Dermatol* 2003;48(4):477–493, quiz 494–496
- 2 Mazereeuw-Hautier J, Hoeger PH, Benlahrech S, et al. Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. *J Pediatr* 2010;157(2):340–342

- 3 Shah S, Frieden IJ. Treatment of infantile hemangiomas with beta-blockers: a review. *Skin Therapy Lett* 2013;18(6):5–7
- 4 Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol* 2008;25(2):168–173
- 5 Blei F, Walter J, Orlow SJ, Marchuk DA. Familial segregation of hemangiomas and vascular malformations as an autosomal dominant trait. *Arch Dermatol* 1998;134(6):718–722
- 6 Haggstrom AN, Drolet BA, Baselga E, et al; Hemangioma Investigator Group. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. *J Pediatr* 2007;150(3):291–294
- 7 Chang LC, Haggstrom AN, Drolet BA, et al; Hemangioma Investigator Group. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics* 2008;122(2):360–367
- 8 Yu Y, Fuhr J, Boye E, et al. Mesenchymal stem cells and adipogenesis in hemangioma involution. *Stem Cells* 2006;24(6):1605–1612
- 9 Barnés CM, Huang S, Kaipainen A, et al. Evidence by molecular profiling for a placental origin of infantile hemangioma. *Proc Natl Acad Sci U S A* 2005;102(52):19097–19102
- 10 Boye E, Yu Y, Paranya G, Mulliken JB, Olsen BR, Bischoff J. Clonality and altered behavior of endothelial cells from hemangiomas. *J Clin Invest* 2001;107(6):745–752
- 11 Walter JW, North PE, Waner M, et al. Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. *Genes Chromosomes Cancer* 2002;33(3):295–303
- 12 Razon MJ, Kråling BM, Mulliken JB, Bischoff J. Increased apoptosis coincides with onset of involution in infantile hemangioma. *Microcirculation* 1998;5(2-3):189–195
- 13 Takahashi K, Mulliken JB, Kozakewich HP, Rogers RA, Folkman J, Ezekowitz RA. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 1994;93(6):2357–2364
- 14 Ritter MR, Moreno SK, Dorrell MI, et al. Identifying potential regulators of infantile hemangioma progression through large-scale expression analysis: a possible role for the immune system and indoleamine 2,3 dioxygenase (IDO) during involution. *Lymphat Res Biol* 2003;1(4):291–299
- 15 Ritter MR, Reinisch J, Friedlander SF, Friedlander M. Myeloid cells in infantile hemangioma. *Am J Pathol* 2006;168(2):621–628
- 16 Metry DW, Hebert AA. Benign cutaneous vascular tumors of infancy: when to worry, what to do. *Arch Dermatol* 2000;136(7):905–914
- 17 Kelly ME, Juern AM, Grossman WJ, Schauer DW, Drolet BA. Immunosuppressive effects in infants treated with corticosteroids for infantile hemangiomas. *Arch Dermatol* 2010;146(7):767–774
- 18 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(24):2649–2651
- 19 Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: follow-up report. *Pediatrics* 2009;124(3):e423–e431
- 20 Izadpanah A, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg* 2013;131(3):601–613
- 21 Price CJ, Lattouf C, Baum B, et al. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. *Arch Dermatol* 2011;147(12):1371–1376
- 22 Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol* 2010;163(2):269–274
- 23 Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propanolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol* 2013;30(2):182–191
- 24 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(2):320–327
- 25 Bagazgoitia L, Hernández-Martín A, Torrelo A. Recurrence of infantile hemangiomas treated with propranolol. *Pediatr Dermatol* 2011;28(6):658–662
- 26 Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics* 2013;131(1):128–140
- 27 Raphaël MF, de Graaf M, Breugem CC, Pasmans SG, Breur JM. Atenolol: a promising alternative to propranolol for the treatment of hemangiomas. *J Am Acad Dermatol* 2011;65(2):420–421
- 28 Blanchet C, Nicollas R, Bigorre M, Amedro P, Mondain M. Management of infantile subglottic hemangioma: acebutolol or propranolol? *Int J Pediatr Otorhinolaryngol* 2010;74(8):959–961
- 29 Pope E, Chakkittakandiyil A, Lara-Corrales I, Maki E, Weinstein M. Expanding the therapeutic repertoire of infantile haemangiomas: cohort-blinded study of oral nadolol compared with propranolol. *Br J Dermatol* 2013;168(1):222–224
- 30 Chakkittakandiyil A, Phillips R, Frieden IJ, et al. Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. *Pediatr Dermatol* 2012;29(1):28–31