

# Use of propranolol in treating hemangiomas

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### Abstract

**Question** I see many children with infantile hemangiomas and have read about new therapeutic options such as propranolol. Is this medication effective and safe for treating hemangiomas in children?

**Answer** Most infantile hemangiomas resolve spontaneously without any need for therapy. In many case series, propranolol has been shown to be effective and safe in treating hemangiomas that cause complications. Further studies are required to determine the optimal dose and duration of propranolol treatment for problematic hemangiomas.

### Résumé

**Question** Je vois souvent des enfants qui ont des hémangiomes infantiles et j'ai lu des articles au sujet de nouvelles options thérapeutiques comme le propranolol. Ce médicament est-il efficace et sécuritaire pour traiter les hémangiomes chez l'enfant?

**Réponse** La plupart des hémangiomes infantiles disparaissent spontanément sans traitement. Dans de nombreuses études de séries de cas, le propranolol s'est révélé efficace et sûr pour le traitement des hémangiomes causant des complications. D'autres études sont nécessaires pour déterminer la dose optimale et la durée du traitement au propranolol dans les cas d'hémangiomes problématiques.

Infantile hemangiomas are the most common vascular tumours in children, occurring in 5% to 10% of infants.<sup>1</sup> Although most are small cutaneous hemangiomas, they can also be large, disfiguring lesions with serious complications. Hemangiomas might also involve the orbit, airway, or visceral organs, such as the liver, brain, intestinal tract, or lungs.<sup>2</sup> They generally become evident within the first days to months of life and are characterized by an initial phase of rapid endothelial cell proliferation during the first year of life and a phase of slow involution.<sup>3</sup>

### Complications

Although most hemangiomas are benign and managed by "watchful waiting," about 10% can cause complications requiring intervention or management by a multidisciplinary team.<sup>2</sup> The most common complication is ulceration, which might result in bleeding, pain, infection, difficulty feeding, and residual scarring.<sup>4</sup> Hemangiomas can cause airway obstruction and visual disturbance depending on their location. A rare complication of hepatic hemangiomas is hypothyroidism secondary to a high level of triiodothyronine deiodinase activity within these hemangiomas.<sup>2</sup> Large hemangiomas can also be associated with high-output heart failure as a result of arteriovenous shunting within the hemangioma.<sup>2</sup> Spinal cord dysraphism and other underlying structural anomalies are associated with segmental hemangiomas in the lumbosacral region. Similarly, extensive lesions on the head and neck can be associated with a spectrum of disease, including posterior fossa malformations, cerebrovascular anomalies, coarctation of the aorta, sternal dysraphism, ocular disease, and airway involvement.

### Management

For most cases of infantile hemangiomas, only parental education and reassurance are required. Hemangiomas with the potential to threaten a child's life or vital functions and those that ulcerate or cause substantial disfigurement warrant treatment. This might include medical or surgical therapy, or a combination of both. The approach to the treatment of a hemangioma should be individualized and based on its location, size, and severity of complications. Complicated hemangiomas are generally managed by pediatric dermatologists, vascular anomalies teams, or other specialists with experience in the field.

Until recently, systemic corticosteroids were the first-line medical therapy for most complicated hemangiomas. Their mechanism of action is poorly understood. The standard treatment regimen is 2 to 4 mg/kg of oral prednisone or prednisolone daily.<sup>2</sup> A meta-analysis<sup>5</sup> reviewed 24 case series of infants who were treated with systemic steroids. The patients received a mean dose of 2.9 mg/kg of prednisone daily for an average of 1.8 months. The response rate was found to be 84%, with the greatest response occurring in children treated in the early proliferative phase of the lesion. Intralesional and topical steroids were found to be useful in small and superficial hemangiomas only.<sup>6</sup>

Alternatives to systemic corticosteroid treatment of aggressive and steroid-unresponsive hemangiomas have included interferon- $\alpha$  and vincristine. Ezekowitz et al<sup>7</sup> found a 90% response rate to interferon- $\alpha$ , an angiogenesis inhibitor, in 20 neonates who failed corticosteroid therapy. However, interferon is rarely used owing to concerns about its side effect profile. One meta-analysis<sup>8</sup>

showed that 11% of 441 patients treated with interferon developed permanent spastic diplegia. Vincristine inhibits microtubule growth, and in a small case report it was used with success in the treatment of corticosteroid-resistant hemangiomas.<sup>9</sup> Its main side effects include constipation and peripheral neuropathy. It is generally administered via a central catheter under the supervision of an oncologist.

Nonpharmacologic treatments of hemangiomas include pulsed-dye laser therapy and excisional surgery. Laser therapy is of benefit only for superficial hemangiomas and might induce ulceration in the early proliferative stage. Surgical excision is effective for complicated localized hemangiomas, depending on the site of involvement, and for correction of cosmetically substantial residual skin changes. Embolization by an interventional radiologist might be considered for hemangiomas in which arteriovenous shunting is causing serious cardiac overload.<sup>9</sup>

### Old medication, new use

Propranolol—a non-selective  $\beta$ -blocker developed in the 1950s by Sir James Black, who was awarded the 1988 Nobel Prize in Medicine—was the first  $\beta$ -adrenergic receptor antagonist found to be useful in clinical medicine.<sup>9</sup>


In 2008, a group of physicians from Bordeaux Children's Hospital in France described an interesting observation from several patients with extensive infantile hemangiomas<sup>10</sup> who received concomitant treatment with propranolol (for obstructive hypertrophic cardiomyopathy and high cardiac output). In each case, the hemangioma regressed upon initiation of propranolol and the children were eventually weaned from corticosteroids without recurrence of hemangioma growth.<sup>10</sup> In the same article, the authors also described similar findings in 9 other children with substantially large hemangiomas whom they treated with propranolol. In a follow-up report, 32 children with complicated hemangiomas treated with propranolol experienced immediate colour changes and effects on growth in all cases,<sup>11</sup> with only one patient discontinuing the drug owing to respiratory wheezing.

The mechanism of action of propranolol is unclear. It is hypothesized that as a  $\beta$ -adrenergic antagonist it induces vasoconstriction, resulting in colour change and palpable softening of the hemangioma, even within 24 hours of treatment,<sup>10</sup> or that propranolol might cause down-regulation of growth factors, such as vascular endothelial growth factor, and up-regulation of cellular apoptosis.<sup>9,10</sup>

Propranolol is generally a safe drug, but it has been associated with adverse events such as bradycardia, hypotension, hypoglycemia, and bronchospasm.<sup>11,12</sup> Lawley et al<sup>12</sup> described a case in which a neonate taking propranolol had a critically low serum glucose level while being completely asymptomatic. They suggested that the  $\beta$ -blockade most likely caused the child to be asymptomatic and, for this reason, they recommended caution in the widespread use of propranolol.<sup>12</sup> Some authors recommend that all

patients should have electrocardiograms and echocardiograms before commencing propranolol therapy to rule out contraindications to  $\beta$ -blockade.<sup>11,12</sup> Slow upward titration of the drug and close monitoring of heart rate, blood pressure, and serum glucose levels have also been recommended in the initial phase of treatment.<sup>11,12</sup>

### Conclusion

Propranolol has recently been found to be efficacious in treating problematic infantile hemangiomas. All the research in this field has been observational thus far. Results of a randomized control trial are awaited to assess the safety, efficacy, and optimal dose and duration of propranolol treatment. Although it appears to be well tolerated in most infants, hypoglycemia is a well-documented adverse effect. The side effect profile of propranolol in this population of infants needs ongoing evaluation. 

#### Competing interests

None declared

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