

## Propranolol Therapy for Infantile Hemangioma

NIVEDITA GUNTURI, \*SRIRAM RAMGOPAL, SUBRAMANIAN BALAGOPAL AND \$JULIUS XAVIER SCOTT

*From the Departments of Pediatrics, #Pediatric Surgery, and \$Pediatric Hemato-Oncology, Sri Ramachandra University, Chennai; India; and, \*Department of Neurology, Boston Children's Hospital, Boston, Massachusetts, United States.*

*Correspondence to: Dr Julius Xavier Scott, Senior Assistant Professor, Head of Pediatric Hemato-Oncology, Sri Ramachandra University, 1, Ramachandra Nagar, Porur, Chennai 600 116, India. jxscott@hotmail.com*

**Context:** There has been widespread interest surrounding the use of beta-blockers (i.e. propranolol, timolol, nadolol, acebutolol) in the treatment of infantile hemangiomas (IH).

**Objective:** To review literature evaluating treatment of IH with propranolol.

**Evidence Acquisition:** We conducted a literature search on PubMed and investigated for case reports, case series, and controlled trials by using search terms including "hemangioma" and "propranolol."

**Results:** Data suggest that beta-blockers are efficacious in cutaneous, orbital, subglottic, and hepatic hemangiomas and assist in the resolution of ulcerated hemangiomas. Improvement has also been documented in children with PHACE syndrome. Propranolol produces favorable results in children who do not respond to steroids and with no long-term adverse effects. Propranolol should be administered with caution due to rare but serious side effects including hypoglycemia, wheezing, hypotension, and bradycardia. Additionally, recurrence of lesions following the cessation of treatment has been documented.

**Conclusions:** Although large-scale randomized controlled trials must be conducted in order to further evaluate the safety and the possible role of propranolol in the treatment of IH, the reviewed literature suggests that propranolol carries promise as a potential replacement for corticosteroids as first-line therapy or as a part of a multimodal approach.

**Key words:** *Beta-blockers, Capillary hemangioma, Infants, PHACE association, Propranolol.*

Infantile hemangiomas (IH) are the most common infantile tumor, with a frequency of 4-10% [1]. Recently, there has been an interest in propranolol and other beta-blockers in the treatment of IH. Propranolol may be more effective and safer than previously established therapies, and may be an alternative when more widely accepted treatments for IH have failed. Initial studies suggest that it may also be used as a first-line therapy. Other selection criteria may include lesion location that is inaccessible to surgery, lesions with a deep component, severe ulceration and/or cosmetic disfigurement, obstruction of airway or visual axis, and the presence of contraindications to other medical therapies. Parental apprehension remains an important indication for treatment in cutaneous IH, irrespective of the possibility of spontaneous involution. In this review, the authors summarize the existing literature concerning propranolol use in IH treatment and provide suggestions for its clinical use and for future areas of study.

### Natural History

IH are benign tumors of the vascular endothelium. The first sign of IH is characteristically an area of pallor that appears several days after birth. The proliferative phase of hemangioma development is characterized by

excessive angiogenesis and occurs over three to six months, whereas the involutinal phase occurs over several years. Although complete involution occurs over months to years [1], IH may remain unresolved. Up to 40% of lesions result in textural changes and fibrofatty scarring [2].

### Diagnosis

A vascular lesion that follows the pattern described is taken to be IH until proven otherwise [2]. If a lesion does not follow the established pattern, diagnosis can be supported by Doppler ultrasound, magnetic resonance imaging (MRI) or angiography [1].

### Locations and Complications

Cutaneous IH can be cosmetically disfiguring and may cause parental apprehension. About 5-13% of cutaneous IH ulcerate [1], which may lead to pain, bleeding and scarring. Glottic IH can extend to the supra-glottic and sub-glottic regions and can partially occlude the airway [3]. Periorbital IH may lead to vision deprivation, astigmatism and strabismus [4]. Involvement of the ear canals may impede hearing. IH involving the viscera or central nervous system may be complicated by hemorrhage, thrombocytopenia, anemia, disseminated

intravascular coagulation and congestive cardiac failure, a constellation of symptoms collectively described as Kasabach-Meritt syndrome. Extensive IH may occur in PHACE syndrome (posterior fossa malformations, hemangiomas, arterial lesions, coarctation of the aorta and other cardiac defects, and eye abnormalities) [1].

### Pathophysiology

IH are clonal expansions of endothelial cells. Genetic mutations in angiogenesis-related protein expression have been identified [5]. Characteristic features of IH include elevated expression of alkaline phosphatase, factor VIII antigen, and cluster of differentiation 31. Elevated expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basal fibroblast growth factor and proliferating cell nuclear antigen may stimulate endothelial growth and lead to dysregulated angiogenesis [6]. The overexpression of glucose transporter 1 (GLUT-1) is specific to IH and is not found in other vascular tumors [7].

### IH Treatment Patterns and Modalities

Treatment for IH may be necessary to a) prevent or improve functional impairment or pain, b) prevent or improve scarring or disfigurement, and c) avoid life-threatening complications. Accepted treatments include intralesional and systemic corticosteroids, chemotherapy (vincristine and interferon alpha), liquid nitrogen cryotherapy, laser ablation and surgical excision [1]. Corticosteroids are currently the preferred therapy for most types of IH.

Recent interest in the use of propranolol in the treatment of IH followed a 2008 report by Leïauteï-Labreïze following an incidental finding [8]. Following several corroborative reports, propranolol therapy was further investigated in a twenty-patient randomized control trial (RCT) [9].

### Mechanism of Action

Several mechanisms of action for propranolol have been suggested. Results from combined grayscale and color Doppler ultrasound imaging suggest that propranolol reduces vessel density [10]. Propranolol has a dose-dependent cytotoxic effect on cultured hemangioma endothelial cells via the hypoxia-inducible factor 1 $\alpha$  pathway, leading to decreased secretion of VEGF [11]. In vitro propranolol decreases plasmalemmal expression of GLUT-1 [12], though no study has evaluated this hypothesis to date with respect to IH. Other possible mechanisms of action include inhibition of matrix metalloproteinases, down-regulation of interleukin-6 and modulation of stem-cell differentiation [11].

### METHODS

We conducted a search on PubMed using combinations of search terms “propranolol”, “hemangioma”, “beta-blocker,” and “beta-antagonist.” All relevant publications from 2009-2012 in all languages were reviewed. Bibliographies of relevant articles were investigated. We reported trial methodology, dosing and investigations, IH localizations, follow-up data, and adverse effects from RCTs, case series, and case reports. Levels of evidence were determined using Oxford criteria ([www.cebm.org](http://www.cebm.org)). In table I, level 3 studies and higher were universally included, and level 4 studies were included if  $n \geq 30$ . Studies were assessed for bias.

### RESULTS

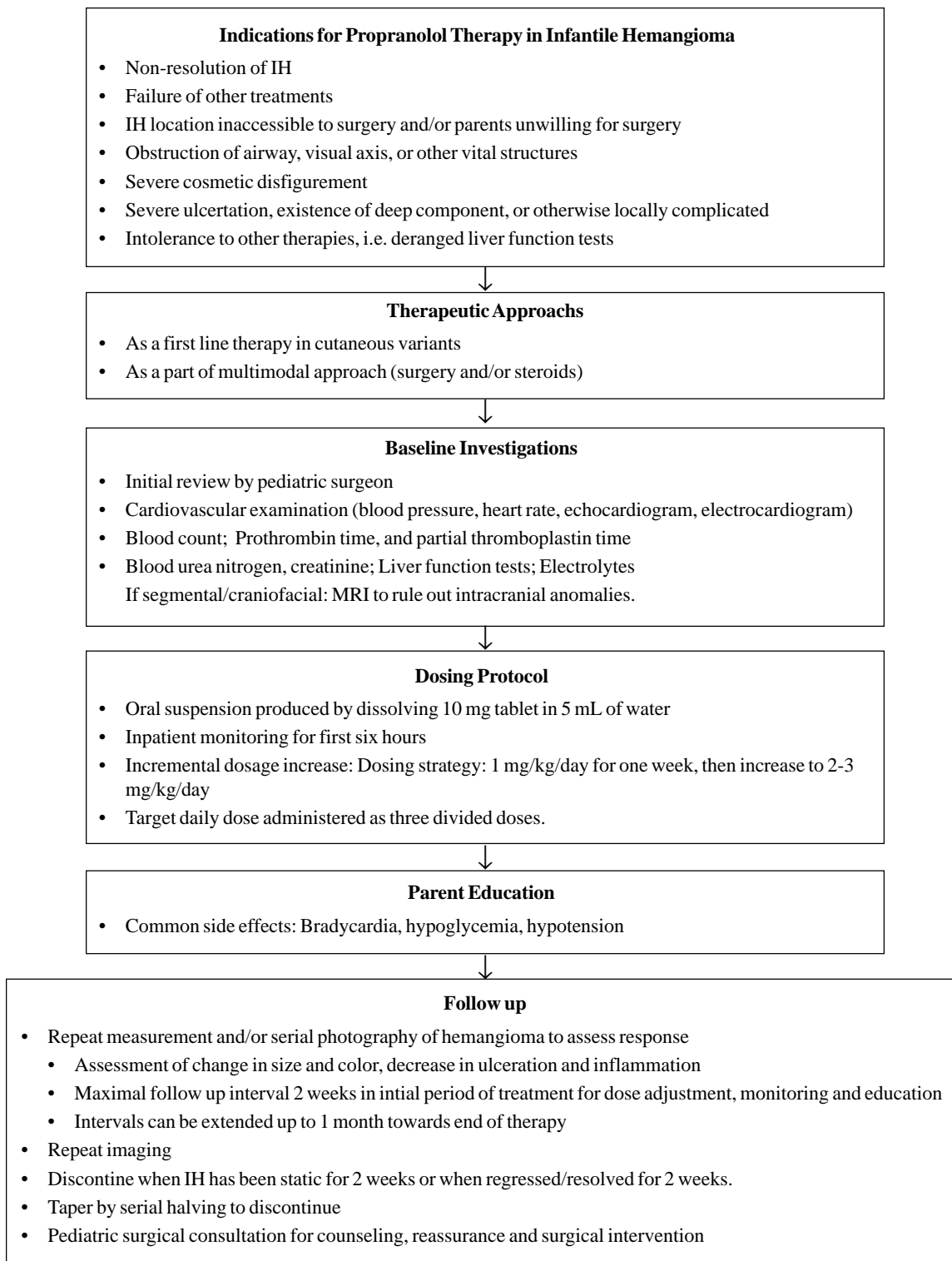
A number of studies have evaluated propranolol in IH (**Table I**). Most investigators did not specify during which phase the treatment took place, though one investigator examined the efficacy of propranolol after the proliferative phase [14]. A few investigators included patients previously treated with steroids [4,8,15-19]. Patients with bronchial asthma were generally excluded. Most investigators increased drug dose to the target over days to weeks [3,9,18,20-24], while others initiated treatment at the target dose [13,15, 25-27]. Some studies used quantitative scores and/or serial photography to assess IH regression [9,13,15, 23, 25, 28]. Treatment was discontinued following either regression or complete resolution. A few investigators followed dose-tapering protocols [3,9,25]. Follow-up was done after treatment discontinuation to monitor for rebound growth. To summarize the information presented in table I, dosages of propranolol ranged from 1.0-3.0 mg/kg/day and the duration of treatment ranged from 1-14 months, the mean duration being 5.85 months. Mean age at treatment was 12.7 months.

### Outcomes

A summary of the larger studies in the literature is provided in **Web Table I**.

*Cutaneous hemangiomas.* Indications for treatment include extensive ulceration, presence of deep component, and cosmetic disfigurement (**Fig.1**). Propranolol reduces color intensity, size and thickness of IH. IH may improve as early as 4 weeks after treatment initiation [15]. Propranolol has been reported to resolve ulcerated IH [18, 26]. Propranolol has been documented to resolve IH resistant to steroid treatment [4,8,15-19].

*Hepatic hemangioma.* Propranolol has been documented to resolve hepatic IH [16]. Therapy can be initiated when steroids are contraindicated, using an incremental dose



**FIG.1** Suggested management approach to infantile hemangioma.

increase and close MRI monitoring. Periodic ultrasonography can also document tumor regression [19]. Propranolol in hepatic IH has been used as late as 10

months after birth [29].

*Orbital hemangioma.* Propranolol treatment is efficacious in the majority of orbital IH [4], occasionally

leading to resolution of proptosis and reduction of astigmatism and amblyopia [4,30].

*Subglottic hemangioma.* Favorable reports in laryngeal IH have been published [17, 31]. Periodic laryngoscopy is required to monitor tumor regression.

*Other hemangiomas.* Propranolol has successfully resolved retroperitoneal [32] and mediastinal [33] hemangiomas. In reported outcomes in children with PHACE syndrome, propranolol caused significant yet incomplete reduction of IH [3,34-37]. The response to propranolol is maximal in the first 20 weeks of treatment and may subside after this [36]. Imaging of cerebral blood vessels should be undertaken before treatment to determine the risk of cerebral ischemia [3].

*Limitations.* Complete treatment failure has been documented [3,31]. IH may undergo rebound growth following cessation of treatment [8,38].

### Adverse Effects

Adverse effects include hypoglycemia, bradycardia, hypotension, and airway hyperreactivity. In an RCT, bradycardia and hypotension were the most common adverse effects [9]. Hypoglycemia may occur secondary to inhibited glycogenolysis, glycolysis and lipolysis [39]. A list of side effects attributed to propranolol use in infants is provided in **Box I**.

### Preterm infants

Propranolol was reported to be effective in a series comprised of seven preterm infants. No side effects, including changes in heart rate or blood pressure, were reported in this group [40]. Similar findings were reported in a series that included six preterm infants [41]. Another published report evaluated propranolol use in 16 very-low birth weight children, of whom nine were born between 27-34 weeks of gestation. Two infants in these series had a fall

in blood pressure within the first six hours of therapy, though this was within physiological limits [42].

### Other beta-blockers

Acebutolol, nadolol and timolol may provide similar efficacy to propranolol in IH treatment. Acebutolol has been used in treatment of subglottic IH [31]. Topical timolol has been effective for cutaneous [20] and ocular [43] IH. Cardioselective beta-blockers may be safer and easier to administer than propranolol.

### Combined propranolol and corticosteroids

In complicated IH, propranolol may be used in combination with corticosteroids for a more rapid response. In one report, a 3-month-old child with a superficial IH obscuring the visual axis was treated with combined propranolol and prednisolone, the latter being gradually withdrawn over one month [44]. In another report, two children with airway-obstructing IH were treated with combined prednisolone and propranolol. After 24 hours, both children were relieved of stridor and steroid was discontinued [45]. These reports suggest that the use of combination propranolol and corticosteroid therapy may provide a valid therapeutic approach to otherwise difficult-to-treat IH.

### Propranolol and surgery

Propranolol may limit the need for surgery in IH. In a multicenter study comparing propranolol to corticosteroid treatment for IH, 12% of children treated with propranolol required surgery, whereas 29% of those treated with steroids required surgery [22]. Surgery still serves a role in IH that are refractory to treatment or that need urgent treatment [35]. Presumably, in patients with an incomplete response to propranolol, medical therapy may limit the extent of surgery necessary for an easy and cosmetically acceptable excision.

**Box I** ADVERSE EFFECTS ASSOCIATED WITH NONSELECTIVE BETA-BLOCKER THERAPY

<i>Metabolic</i>	<i>Pulmonary</i>
Hypoglycemia [22, 39]	Wheezing [13, 20, 24]
<i>Cardiac</i>	Stridor [15]
Bradycardia [15, 20, 49]	RSV exacerbation [9, 50]
Hypotension [13, 20, 21, 28]	<i>Gastrointestinal</i>
Tachycardia [22]	Diarrhea/GI upset [18, 28, 34, 49]
<i>Central Nervous System</i>	Gastroesophageal reflux [21, 24, 26, 34]
Agitated sleep [9, 15, 18, 21, 26, 28, 30, 49]	<i>Other</i>
Insomnia [13]	Cold palms [13, 24, 26]
Drowsiness [18, 23, 24, 30, 38]	Night sweats [13]
Crying episodes/Anxiety [30]	Skin changes [22, 24, 50]
Hypotonia [23]	

### Route of administration

The route of administration of propranolol in the majority of published studies is via oral ingestion. Propranolol is available in 10mg and 40mg tablets which can be dissolved in water for easy administration. Parents should be advised to soak the tablets in 10ml of water for one minute before crushing and not to filter the suspension [46].

Intralesional drug injection also causes regression of periorbital IH [47]. The use of a 1% ointment applied for cutaneous IH led to regression in 85% of patients in a case series [40]. Topical treatments may result in fewer adverse effects.

### Limitations

Most reviewed studies provided level 4 evidence. They may be subject to selection bias. Many of the studies did not use objective measurement methodologies to evaluate the efficacy of treatment.

### Recommendations

We have suggested a tentative treatment regimen (**Fig. 1**). The choice between in-hospital and outpatient treatment should be made on a case-by-case basis [48]. The child's age, history of prematurity, hemangioma subtype and location, comorbidities, and the level of parental understanding should be considered. Abdominal ultrasonogram should be obtained for visceral IH to check for hepatic artery and portal vein dilatation. Patients with PHACE syndrome should undergo cerebral angiography to rule out cerebral ischemia. Parental education should include discussion of the warning signs of hypoglycemia and should emphasize the importance of maintaining a regular feeding schedule. A pediatric surgical opinion should be sought, and parents should be informed of the possibility of surgical excision if therapy fails. In addition, downgraded IH or fibrofatty remnants can be excised more effectively following propranolol therapy. Special consideration should be made for premature infants, unusual or high-risk locations, and patients with Kasabach-Merritt syndrome. Regression of IH should be monitored by serial photography. The above protocol should be evaluated by randomized, large-scale trials.

### CONCLUSION

Case reports have documented the successful use of propranolol in the Indian setting [19, 37]. Considering the challenges of assuring patient compliance and maintaining close follow-up in India, it is inadvisable to promote propranolol therapy except in cases where careful and close monitoring of patient parameters is feasible.

Propranolol can be tried as first-line therapy in IH irrespective of age, location, extent and phase of growth. Treatment might also be helpful in downgrading the size and local complications of IH, making the lesion more amenable to surgical excision. Due to the lack of long-term side effects and its high response rate, propranolol therapy may prove to be superior to existing therapies. More extensive prospective double-blinded RCT of propranolol therapy must be carried out and reported by pediatricians and pediatric surgeons in order to establish its efficacy conclusively.

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