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Review

Beta blocker treatment for infantile hemangiomas

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Abstract

Infantile hemangiomas (IH) are common childhood vascular tumors. Treatment of IH has undergone rapid change in recent years. Since 2008, oral propranolol has been used to treat complicated IH and has proven superior to previously used therapies. More recently, the efficacy of other systemic beta blockers, specifically atenolol and nadolol, has been reported. In addition, topical timolol solution has been effective for treatment of smaller, more superficial IH. The purpose of this article is to review the current literature of beta-blocker therapy for IH.

Keywords: Beta blocker, propranolol, atenolol, nadolol, timolol, infantile hemangioma

Introduction

Infantile hemangiomas (IH) are the most common benign vascular tumors in children, with an incidence of 4-10% in infants [1, 2]. The natural course of IH is rapid proliferation during the first few weeks or months of life, followed by a plateau period, and then involution over several years [3]. Most involute spontaneously without treatment; 90% of IH completely regress by 9 years of age [4]. However, approximately 10% of IH require intervention to prevent or treat complications such as functional impairment, disfigurement, scarring, and painful ulceration [5].

Traditionally, oral corticosteroids were the treatment of choice despite varied efficacy and frequent, serious adverse events [3]. Preferred first-line therapy quickly shifted after the 2008 publication by Léauté-Labrèze *et al*. describing the dramatic effect of oral propranolol on IH involution discovered while treating two children with high output cardiac failure [6]. Since then, many articles have reported favorable results with propranolol in IH. Propranolol was found to be safer, more tolerable, and more effective than previously used corticosteroids. However, propranolol does have risks and serious potential adverse effects include hypotension, bradycardia, hypoglycemia, and bronchospasm. The mechanism of beta-blocker therapy for IH is not fully understood. Rapid vasoconstriction, inhibition of angiogenesis, induction of apoptosis, and decreased renin production may play a role [3].

Propranolol is a lipophilic non-selective beta blocker that crosses the blood brain barrier. The beta-adrenergic system plays a role in memory modulation and novelty detection; the potentially harmful long-term effects of beta-blocking agents on the central nervous system (CNS) in infancy are unknown [7]. More recently, atenolol and nadolol have been studied as alternative systemic beta blockers for treatment of IH. These drugs do not cross the blood brain barrier, theoretically eliminating the potential risk of CNS effects, such as sleep disturbance and future memory deficits. Compared to propranolol, less frequent dosing is required for atenolol (once daily) and nadolol (twice daily), which may increase patient compliance [7, 8, 9].

Atenolol is a hydrophilic cardioselective beta blocker that acts primarily as a β1-receptor antagonist and spares β2-receptors. Therefore, bronchospasm and hypoglycemia associated with β2 blockade are essentially negated with atenolol [8, 9]. Nadolol is a hydrophilic non-selective beta blocker. In contrast to propranolol, nadolol has less myocardial depressant activity and a longer half-life (12-24 hours), which decreases rebound growth [7]. The topical β-blocker timolol is an alternative to oral propranolol for smaller, more superficial IH to reduce the risks of adverse events associated with systemic therapy [10, 11, 12]. The purpose of this article is to review the current literature of beta-blocker therapy for IH.

Methods

In October 2014, four PubMed searches were performed using the terms [‘Infantile hemangioma’] AND [‘propranolol’], [‘atenolol’], [‘nadolol’], or [‘timolol’]. Propranolol and timolol searches were limited to clinical trials or randomized controlled trials. In addition, three propranolol articles included in this review were PubMed related citations.

Articles written in Chinese were excluded. The authors of articles that could not be accessed were contacted; those that did not respond were excluded from this review.

Study design, year(s) the study was conducted or year of publication, duration of therapy, number of patients treated with beta blocker, mean age at treatment initiation, IH location and type, beta blocker dose, divided daily dose or frequency, outcome/efficacy, adverse events, and number of patients with rebound/regrowth after treatment completion were recorded for each study. Not all variables were reported in every study.

RESULTS

A. Oral propranolol

Twenty-two articles describing the efficacy of propranolol in the treatment of infantile hemangiomas were included in this review (Table 1) [8,13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. Despite a lack of uniformity or standardization with measured outcomes, several observations including dose, overall response, response time, and rebound occurrence can be made. The most commonly used propranolol dose was 2 mg/kg/day divided TID; although many variations have been reported from 0.75-4 mg/kg/day divided BID-TID. Overall, mean age of patients treated during the proliferative phase was 5 months. Six studies reported treatment of IH after the proliferative phase ranging from 11-31 months of age.

Overall, 15 studies reported a 100% response rate to oral propranolol. Of the studies that did not report a 100% response rate, non-responders ranged from 3-10%. There appears to be an association between age at treatment and IH response, with Sondhi et al. reporting 100% response in patients less than 6 months, 89% response in patients aged 6-36 months, and 0% response in patients older than 36 months [19]. Additionally, Fuchsmann et al. cited the two treatment failures occurring in patients with delayed treatment [31]. Response time was not reported in all studies, but several studies report softening and lightening of color within 24-48 hours [13, 16, 17, 21]. Holmes et al. reported 100% cessation of proliferation at 2 weeks with regression in 55% of IH during that same period [23]. Similarly, Léauté-Labrèze et al. reported 100% cessation of proliferation after 1 month of treatment [13]. Furthermore, Zvulunov et al. showed that addition of propranolol during IH involution in patients with a mean age of 28 months led to increased involution rates [33].

Mean duration of therapy ranged from 1-14 months, with an average of 7 months. Interestingly, Sondhi et al. reported that treatment after 20 weeks duration was associated with no further significant response [19]. Rebound or recurrence was seen in 13 studies with rates ranging from 2.5% to 40%. Overall, the majority of rebounds was characterized as re-coloration and mild regrowth and was reported to be successfully retreated with oral propranolol. Three studies reported zero recurrence or rebound [16, 19, 22]. Ma et al. associated recurrence with early discontinuation of propranolol after only 4-5 months [20].

Ulcerated hemangiomas were specifically reported on by 6 authors. Several publications cited healing of ulcerations anywhere from 2 weeks to 2 months [17, 21, 27, 31]. Manunza et al. reported rapid resolution in small ulcerations compared to limited resolution in larger ulcerations [30]. Additionally, Hermans et al. noted that 70% of patients with an ulcerated IH treated after 3.5 months of age had ulcer duration beyond 8.7 weeks of treatment [28]. Furthermore, Saint-Jean et al. commented that ulcerated hemangiomas on the head and neck resolved faster than those located elsewhere. Only Saint-Jean et al. reported recurrence of ulceration during rebound. However, they noted resolution of ulceration with re-administration of oral propranolol [27].

Table 1. Oral Propanolol

Study	Study design	Year	Duration of therapy	# of patients treated	Age*	IH location & type	Dose (mg/kg/d)	Divided daily dose	Outcome/Efficacy	Adverse events	Rebound/Regrowth
Léauté-Labrèze et al.	Monocenteric double-blinded randomized placebo-controlled trial	2008-2010	1 mo	6	3 mos	Various locations	3 for 15 days and then 4 for 15 additional days	N/A	Within 1 month, IH growth stopped and significant involution ensued in all propranolol-treated patients. In the propranolol group, IH thickness decreased by a mean of 45% (compared to a mean increase of 11% in the placebo group), and IH size decreased by a mean of 16% (compared to a mean increase of 9% in the placebo group). Within 24 hrs of propranolol initiation, softening and color change from intense red to purple was noted, with continued improvement throughout treatment.	Drowsiness (1), asymptomatic mild decrease in heart rate and diastolic blood pressure	N/A
Hogeling et al.	Double-blinded, randomized placebo-controlled parallel-group trial	2009-2010	6 mos	19	17 mos	Various, mostly facial	2	3	60% decrease in tumor volume (compared to 14% in the placebo group). In the propranolol group, IH growth stopped by week 4, and there was a significant decrease in redness and elevation at weeks 12 and 24 compared to the placebo group. A significant difference in percent change in volume between the groups was found at all weeks, with the largest difference at week 12.	Upper respiratory tract infection (1), bronchiolitis (4), viral gastroenteritis (1), streptococcal infection (1), cool extremities (1), dental caries (1), sleep disturbance (2)	Not formally assessed, but mild rebound redness and growth was seen.
Bauman et al.	Multi-institutional investigator-blinded randomized placebo-controlled trial	2010-2012	11 mos*	9	3 mos	Various	2	3	64% decrease in the mean total surface area at 4 mos of treatment	Dehydration (1), asymptomatic hypoglycemia after the first dose only (1). Some patients had asymptomatic BP decreases that resolved spontaneously, and there was an increased incidence of upper respiratory tract infections.	22% (2/9)
Malik et al.	Randomized controlled trial	2011-2012	10 mos*	10	5 mos	Various, mostly head and neck and superficial	2*	2	According to geometric measurements, maximum reduction occurred in the propranolol group in the first 3 mos with a mean reduction of 36 ± 21%. All IH's continued to decrease in size at 6, 12 and 18 mos. Mean size reduction (%) ± SD based on VAS: At 3 mos: 58 ± 20 At 6 mos: 71 ± 18 At 12 mos: 85 ± 11 At 18 mos: 90 ± 10 Mean initial response time was 4 ± 3 days. There was significant early IH flattening, change in consistency within 24 hrs, and color fading within 48 hrs. All IH's continued to fade in color compared to baseline.	Asymptomatic hypoglycemia at the start of treatment (1), somnolence (1)	None
Ábarzúa-Araya et al.	Double-blinded randomized controlled trial	2012-2013	6 mos	10	5 mos	Various	2	3	60% complete response (complete resolution; residual telangiectasia and redundant tissue were considered complete response); 40% partial response (any improvement in size, color, or consistency that did not meet complete response criteria)	None	40% (4/10); all responded to reintroduction of propranolol
Sans et al.	Prospective clinical study	Published in 2009	6 mos*	32	4 mos for early intervention (27 pts); 31 mos for late intervention (5 pts)	Various	2-3	2 or 3	Propranolol efficacy was 100%. In all IHs, softening and color change from intense red to purple was observed within 24 hrs, with continued improvement thereafter. Ulcerations completely healed in <2 mos. In the 11 patients who had ultrasound exams, results showed 40% mean regression	Wheezing/Asthma onset (1), Blood pressure decrease 3 hrs after first dose that resolved spontaneously (1), Insomnia (2), Agitation (2), Nightmares (1), Profuse sweats (1),	4/16 mild recoloration 3/16 mild regrowth; 2 patients restarted treatment with good results

									in maximal thickness and a 27% increase in mean resistivity index, indicating lower vascular activity within the IH.	Cold hands (1)	
Vercellino et al.	Prospective clinical study	2008-2010	6 mos*	68	Group A: <12 mos (mean 7 mos) [36 pts] Group B: >12 mos (mean 19 mos) [32 pts]	Various	2*	3	In 93% of patients, propranolol was successful in stopping proliferation and accelerating involution of IHs. In the majority of cases, decreased redness and palpable softening was noted within a few days of starting treatment. Decreased volume was observed in many cases after 1-2 weeks of propranolol. Continued improvement was seen, with some hemangiomas becoming nearly flat in 6-8 weeks. Age < 12 mos: 34/36 (94%) patients had marked improvement after the first month. Age > 12 mos: 21/32 and 8/32 (91%) patients had marked and moderate improvement respectively after the first month. 3/32 patients showed no improvement. Propranolol was ineffective in 7% of patients.	None	1 month after discontinuation: recoloration or mild regrowth in 24% (16/68); moderate-to-severe regrowth in 15% (10/68)
Sondhi et al.	Single-center, historically-controlled prospective open-label trial	2009-2011	8 mos*	31	11 mos	Various	2	2	28/31 (90%) propranolol-treated patients had >50% involution of IH, compared to only 4/14 (29%) untreated patients in the control group. Propranolol-treated patients demonstrated significantly faster and greater degree of IH involution compared with no treatment. The overall mean score for propranolol-treated patients (4.4) was significantly better than untreated patients (8.4). 3 patients (10%) did not improve with propranolol despite 12 wks of therapy. Response to Propranolol: 20/20 (100%) patients ≤ 6 mos of age 8/9 (89%) patients 6 - 36 mos of age 0/2 (0%) patients > 36 mos Decrease in size and redness was most pronounced in the first 8 weeks, with 65-80% of involution during this time. From 8 to 20 weeks, statistically significant reduction in IH was also noted. Beyond 20 weeks, response to propranolol was statistically insignificant.	Insomnia (2), bronchospasm (1)	None at the 6 month follow-up visit
Ma et al.	Prospective, interventional case series	2009-2011	14 mos*	89 (Chinese)	4 mos	Various locations	0.75-1	2	During the first week, superficial lesions changed color from intense-red to red or purple, and subcutaneous lesions changed in texture from hard to medium. After 3 months, most IHs regressed with further improvement in color (purple with areas of gray) and texture (soft). After 6 months, complete regression was noted in parts of the IHs. After 6 months: 44/89 (50%) patients had excellent response (76-100% regression) 21/89 (24%) patients had good response (51-75% regression) 24/89 (27%) patients had fair response (26-50% regression) 0/89 (0%) patients had poor response (0-25% regression)	Mild diarrhea that resolved spontaneously by the end of the first week (3), restless sleep (1), nausea (2), cold extremities (1), slight hypoglycemia (4), slightly elevated ALT and AST (5)	4.5% (4/89), all of whom discontinued propranolol treatment after 4–5 months.
Celik et al.	Prospective clinical	2009-2011	8 mos*	67	7 mos	Various	2	2	Within 24 hrs of propranolol initiation, all patients	None	2 wks after stopping propranolol, 10

	study								demonstrated color fading and softening of IHs. Rapid shrinkage and fading continued during the first month. Thereafter, a slower rate of involution was observed, with the majority of IHs becoming pale and nearly flat within 6 -12 mos. Total involution occurred in 7 IHs. Superficial IHs: 90% (± 8, 70-100%) decrease in volume Combined IHs: 79% (± 11, 54-94%) decrease in volume 13/14 ulcerated IHs healed within the first month.		patients had mild regrowth, which regressed spontaneously by 4 wks
Kagami et al.	Prospective study	2010-2012	9 mos*	15	3 mos	Various	2	3	Compared to the laser and/or cryosurgery control group, propranolol treatment demonstrated significantly shorter time from initiation of therapy to growth arrest [median 41 (range, 11–147) vs. 14 (7–53) days], start of shrinking [93 (11–151) vs. 21 (7–95) days], and start of color regression [63 (11–98) vs. 21 (7–72) days].	None	None during the 56–287 day post-treatment follow-up
Holmes et al.	Prospective clinical study	First published in 2010	3 mos*	31	4 mos	Various	3	3	Proliferation quickly ceased in 100% of IHs, and significant regression occurred in 87%. Palpable softening, color change, and proliferation cessation occurred within 48 hrs in 74% (23/31) of patients. Proliferation ceased by 2 wks in the remaining 26% (8/31) of patients. Regression was noted within 2 wks in 55% (17/31) of patients, within 4 wks in 16% (5/31) of patients, and within 10 wks in 16% (5/31) of patients. 13% (4/31) of IHs remained stable in size,	Transient asymptomatic hypotension during a propranolol loading dose that resolved before the subsequent dose (1), gastroesophageal reflux (1), restless at night (1), bronchiolitis (1)	24% (6/25); retreatment with propranolol was effective in all patients

									without evidence of regression. 3 of the 4 patients with stable IH were >9 mos old. Ulceration epithelialization was seen in 7/8 patients within 3 wks of treatment. The other ulcerated IH was only treated for 1 wk.		
Corapcioğlu et al.	Prospective clinical study	Published 2011	6 mos*	12	8 mos	Various	2	3	At the 2ND month of propranolol therapy, the regression rate of the mean dimension of the IH was 38 ± 15% (range 15-50%, median 45%). Over 9 months, the regression rate of the mean dimension of the IH was 55 ± 31% (range 20-80%, median 50%).	Transient bradycardia which improved spontaneously (1)	N/A
Talaat et al.	Prospective clinical study	Published 2012	7 mos*	50 infants; 80 IHs	6 mos	Various	2	3	Size regression: Excellent: 60 (75%) Good: 15 (19%) Fair: 5 (6%) Poor: 0 (0%) No response: 0 (0%) Color clearance: Before treatment: 153 ± 22 After treatment: 42 ± 13 Sonographic assessment: Thickness (mm) Before treatment: 9 ± 9 After treatment: 4 ± 7 Resisting index Before treatment: 0.6 After treatment: 0.8 Color changes, softening and size regression occurred, with IHs becoming nearly flat by the end of treatment.	Ulceration and scarring (1 IH); residual and/or recoloration (5 IHs); epidermal atrophy (2 IHs); telangiectasia (6 IHs); residual fibrofatty tissue (10 IHs)	2.5% (2/80) regrowth
Price et al.	Multicenter retrospective case series	2005-2010	8 mos*	68	5 mos	Various	2	2	56/68 propranolol-treated patients (82%) demonstrated ≥ 75% clearance compared with 12/42 patients (29%)	Hypoglycemia (1), nonspecific skin eruption not associated	2/68 (3%) Both pts responded to reinitiation of propranolol

									who received oral corticosteroids.	with propranolol therapy (2)	
Saint-Jean et al.	Multicenter, retrospective, observational study	2008-2009	6 mos*	33	5 mos	Ulcerated	2-3	2 or 3	The average time for complete ulceration healing was 5.7 weeks (range, 5 days-8 months) in all propranolol-treated patients. Ulceration healing required ≥12 weeks in 3 patients. Excluding these 3 outliers, the average time for complete ulceration healing was 4.3 weeks. Head and neck ulcerated IHs healed significantly faster than those located in other areas (4 vs. 7.6 weeks, respectively). Complete pain control was achieved in 14.5 days (range, 1-60 days).	Nightmares (5), esophageal reflux (1), cool hands and feet (1)	4/29 (14%) had recurrence of ulceration; reintroduction of propranolol led to complete healing
Hermans et al.	Case series with matched historical controls	2008-2010	9 mos*	20 pts; 78 IHs	4 mos	Ulcerated	2-2.5	3	The average ulceration duration was significantly shorter for the propranolol group (9 wks) compared with the control group (22 wks). A shorter time for complete ulceration healing was noted in patients starting propranolol at a younger age. 7/10 (70%) patients who started propranolol at >3.5 mos of age had an ulceration that lasted >8.7 weeks compared with only 2/10 (20%) of patients who began treatment at an earlier age. In all patients, reduced redness and tenseness occurred within the first 3 days and continued throughout treatment. In most patients, pain decreased within a few days of starting propranolol.	Drowsiness/tiredness (6), restless sleeping (2), cold extremities (6), poor feeding (2), gastrointestinal complaints (diarrhea, vomiting) (1)	4/19 (21%) had partial regrowth and slightly increased redness; no recurrence of ulceration
Buckmiller et al.	Retrospective single institution case series	2008-2009	Treated until 12 mos old, unless in the involutional phase (treated at least 6 mos and until benefit ceases)	32	7 mos	Various	2	3	97% (31/32) improved with propranolol. 16/32 (50%) excellent responders: no additional therapy needed. Four of these patients achieved complete resolution without signs of residual disease. 15/32 (47%) partial responders: decreased size and growth but had adjuvant therapy before or after propranolol. 1/32 (3%) non-responder: persistent growth.	Somnolence (6), gastroesophageal reflux (2), allergic rash (1), respiratory syncytial virus exacerbation (1)	20% (1/5) that had completed therapy
Manunza et al.	Case series	2008-2009	8 mos*	30	6 mos	Head and neck	2	3	Softening, color fading, and growth cessation occurred in all IHs. 26/30 patients responded within 1 wk, and the other 4/30 responded within 1 mo. All IHs showed continued improvement thereafter. There was rapid healing of small superficial ulcers, but limited response of larger deeper ulcers. In 2 patients, ulceration worsened.	Asymptomatic isolated systolic blood pressure < 70 mmHg that normalized later that day (3)	N/A
Fuchsmann et al.	Multi-institutional retrospective study	2008-2009	9 mos*	39**	4 mos for early treatment (33 pts); 29 mos for late treatment (6 pts)	Head and neck	2-3	3	37/39 IHs treated with propranolol had lightening of color and reduction in size within 2 weeks. Softening and healing of ulcerations also occurred within 2 weeks. In the 16 patients who had ultrasound exams, results showed decreased hemangioma thickness and vascular activity. 2/39 hemangiomas (subglottic and nasal tip) had no response or partial response. In both of these cases, propranolol treatment was delayed and given after other treatment failures.	Trouble sleeping (5), mild diarrhea (2)	4/30 mild recoloration 6/30 regrowth; propranolol was effective with reinitiation.
Bagazgoitia et al.	Multicenter retrospective case	2008-2009	5 mos*	71	6 mos	Various	2	2	Average IH reduction (size and color): 32% at 4 wks	Agitated sleep (10), stridor (1)	N/A

	series								44% at 8 wks 52% at 12 wks 56% at 16 wks 61% at 20 wks 65% at 24 wks 65% at 28 wks 68% at 32 wks Number of IHs with ≥50% reduction in severity: 8/71 (11%) IHs at 4 weeks 24/71 (34%) IHs at 8 weeks 42/71 (59%) IHs at 16 weeks		
Zvulunov et al.	Multicenter retrospective case series	2009	4 mos*	42	28 mos	Post-proliferative phase; predominantly mixed type	2*	N/A	In all patients, the rate of involution significantly increased with propranolol, compared with the rate of involution during active nonintervention before treatment. VAS reduction rate before treatment was 0.4/month compared to the accelerated rate of 0.9/month during propranolol treatment. Mean VAS score of 6.8 before treatment was reduced to 2.6 during treatment.	Sleep disturbance (2), somnolence (1), transient dyspnea (1)	N/A

Comments:

* = mean

VAS (Visual Analogue Scale)

Reported adverse events during oral propranolol therapy included asymptomatic hypoglycemia, asymptomatic decreases in blood pressure and heart rate, bronchospasm, wheezing, transient dyspnea, stridor, sleep disturbance, insomnia, somnolence, cool extremities, sweating, gastroesophageal reflux, gastrointestinal complaints (nausea, vomiting, diarrhea), slightly elevated ALT and AST, allergic rash, increased incidence of upper respiratory infections, bronchiolitis, viral gastroenteritis, streptococcal infection, dehydration, and dental caries. Four of the twenty-two studies reported no adverse events with propranolol treatment.

B. Oral atenolol

Only two studies, retrievable in PubMed, have been published describing the efficacy of oral atenolol in the treatment of IH (Table 2). Both studies compared atenolol to propranolol. In a randomized, double-blinded control trial, Ábarzúa-Araya et al. studied 13 patients with IH treated with atenolol for 6 months compared to 10 patients treated with oral propranolol for 6 months. The average age of patients at treatment initiation was 5 months in both arms [8]. In a prospective cohort study by de Graaf et al., 30 infants with IH treated with atenolol were compared with a historical propranolol-treated control group. The average duration of atenolol treatment was 12 months, and the average age at the time of atenolol initiation was 6 months. Of note, atenolol-treated patients were significantly younger than propranolol-treated patients [9]. Both studies report a daily dosing regimen; however, Ábarzúa-Araya et al. used 1 mg/kg/day while de Graaf et al. ranged from 1-3 mg/kg/day, with an overall average of 1.2 mg/kg/day [8, 9].

With regards to response rates, Ábarzúa-Araya et al. showed a 54% complete response compared to 60% of the patients on oral propranolol. A complete response included residual telangiectasia and redundant tissue [8]. de Graaf et al. reported no significant difference in the quantitative improvement values for the two treatment groups. They reported a 90% response rate of clinical involution for atenolol-treated patients at 2 weeks compared to a 100% response rate for propranolol-treated patients [9]. Ábarzúa-Araya et al. reported 2 patients with rebound growth after discontinuation of atenolol that responded to re-treatment [8]. de Graaf et al. did not comment on recurrence or rebound.

Only de Graaf et al. commented on the use of atenolol for ulcerated IH. Of these 8 patients, only 2 showed an inadequate response to oral atenolol at 2 weeks. One of these patients had previously failed oral propranolol.

Table 2. Oral atenolol

Study	Study design	Year	Duration of therapy	# of patients treated	Age*	IH location & type	Dose (mg/kg/d)	Divided daily dose	Outcome/Efficacy	Adverse events	Rebound/ Regrowth
Ábarzúa-Araya et al.	Double-blinded randomized controlled trial	2012-2013	6 mos	13	5 mos	Various	1	1	54% complete response (complete resolution; residual telangiectasia and redundant tissue were considered complete response); 46% partial response (any improvement in size, color, or consistency that did not meet complete response criteria)	None	15% (2/13); both responded to reintroduction of atenolol
de Graaf et al.	Prospective cohort study	2010-2011	12 mos*	30	6 mos	Various	1*	1	90% (27/30) of patients showed clinical involution (softening, color change, and size reduction) at 2-8 wks. 2/8 ulcerated IHs had insufficient response after 2 wks of treatment. There was no significant difference in VAS scores or ΔHAS between the atenolol and propranolol groups.	Diastolic BP below the 5th percentile for age (1), Transient restless sleep (8), Constipation (2), Diarrhea (2), Cold extremities (some)	N/A

Comments:

*= mean

VAS (Visual Analogue Scale); HAS (Hemangioma Activity Score)

According to de Graaf et al., only 3% (1/30) of patients treated with atenolol had severe adverse effects (hypoglycemia, bronchial hyperreactivity, or hypotension), compared with 25% (7/28) of propranolol-treated patients. Mild adverse effects (restless sleep, constipation, and diarrhea) were reported in 40% (12/30) of atenolol-treated patients, compared with 50% (14/28) of propranolol-treated patients [9]. In contrast, Ábarzúa-Araya et al. reported no adverse events for patients treated with atenolol or propranolol [8].

C. Oral nadolol

One study, Pope et al., describing the efficacy of oral nadolol in the treatment of IH (Table 3) was found on PubMed. The study compared nadolol 2 mg/kg/day divided twice daily to propranolol 2 mg/kg/day divided three times daily in an assessor-blinded cohort study of 19 patients with head and neck IH. Treatment duration in both arms was 6 months. Using a Visual Analogue Scale (VAS), they found mean percentage IH shrinkage was 51 ± 18% at 4 weeks, 83 ± 14% at 12 weeks, and 97 ± 3% at 24 weeks for nadolol-treated patients, compared to 28 ± 10% at 4 weeks, 56 ± 17% at 12 weeks, and 86 ± 15% at 24 weeks for propranolol-treated patients. Compared to propranolol, nadolol had a faster and more favorable effect on IH. There was a significant difference in IH involution between the nadolol and propranolol groups at the end of treatment. Six months of oral nadolol treatment led to nearly complete involution of IH. There was no comment on rebound or regrowth in this study.

Table 3. Oral nadolol

Study	Study design	Year	Duration of therapy	# of patients treated	Age*	IH location & type	Dose (mg/kg/d)	Divided daily dose	Outcome/Efficacy	Adverse events	Rebound/ Regrowth
Ábarzúa-Araya et al.	Double-blinded randomized controlled trial	2012-2013	6 mos	13	5 mos	Various	1	1	54% complete response (complete resolution; residual telangiectasia and redundant tissue were considered complete response); 46% partial response (any improvement in size, color, or consistency that did not meet complete response criteria)	None	15% (2/13); both responded to reintroduction of atenolol
de Graaf et al.	Prospective cohort study	2010-2011	12 mos*	30	6 mos	Various	1*	1	90% (27/30) of patients showed clinical involution (softening, color change, and size reduction) at 2-8 wks. 2/8 ulcerated IHs had insufficient response after 2 wks of treatment. There was no significant difference in VAS scores or ΔHAS between the atenolol and propranolol groups.	Diastolic BP below the 5th percentile for age (1), Transient restless sleep (8), Constipation (2), Diarrhea (2), Cold extremities (some)	N/A

Comments:

*= mean

VAS (Visual Analogue Scale); HAS (Hemangioma Activity Score)

Reported adverse events during nadolol treatment included cold extremities, gastrointestinal symptoms, sleep disturbance, and cold-induced wheezing. Additionally, asymptomatic decrease in heart rate from a mean of 139 ± 14 beats per minute (bpm) to 115 ± 11 bpm was recorded [7]. Adverse events of propranolol treatment and rebound growth were not included in the study.

D. Topical timolol

Three studies describing the efficacy of topical timolol in the treatment of IH (Table 4) were retrieved from PubMed. All studies report BID application; however, timolol concentration differed (0.1, 0.25, or 0.5%). Treatment duration ranged from 2-6 months, and average age at treatment initiation was 2-8 months.

According to Chan et al., there was a marginally significant difference in IH size between timolol and placebo groups at 12 and 16 weeks, with smaller IH in the timolol group. At 8, 20, and 24 weeks, the timolol-treated patients had significantly more IH with ≥ 5% volume reduction. Additionally, the timolol group had significantly more photos scoring 0 (no redness) and fewer photos scoring 2 (completely red) [10]. Results from Chakkittakandiyil et al. showed improvement in 99% (72/73) of patients, with a mean VAS improvement of 45 ± 30%. The only patient who did not improve was a 4-month-old male with a mixed IH that increased in size during 2 weeks of treatment with timolol 0.5% solution [11]. Chambers et al. found IH color improved in all timolol-treated patients, and IH thickness decreased in 12/13 patients. Superficial (n = 5; 100% good response) and mixed (n = 7; 43% good response, 57% moderate response) IH decreased in size; the one deep IH increased in size (poor response) despite topical timolol treatment [12]. Overall, Chan et al. found topical timolol was more effective for IH with a mean diameter <11.3 mm [10], and Chakkittakandiyil et al. reported better response in superficial IH, with 0.5% concentration, and with treatment duration longer than 3 months [11].

TABLE 4: Topical Timolol

Study	Study design	Year	Duration of therapy	# of patients treated	Age*	IH location & type	Dose	Frequency	Outcome/Efficacy	Adverse events (#patients)	Rebound/ Regrowth
Chan et al.	Double-blinded, randomized placebo-controlled, parallel-group trial	2011-2012	6 mos	15	2 mos	Various locations Superficial	1 drop of 0.5% gel	BID	Comparing timolol and placebo groups, there was a marginally significant difference in IH size at 12 and 16 wks (with smaller IHs in timolol-treated patients) and a significant difference in †blinded photo score distribution at 24 wks.	None	Post-trial follow-up of most patients showed no significant rebound
Chakkittakandiyil et al.	Multicenter retrospective cohort study	First published in 2011	3 mos*	73	8 mos	Mostly head and neck Mostly superficial	62/73 treated with 0.5% gel-forming solution 11/73 treated with 0.1% gel-forming solution	BID	72/73 (99%) patients improved; mean VAS improvement was 45 ± 30% at the last follow-up appointment.	Sleep disturbance (1)	None at 3–6 mos follow-up
Chambers et al.	retrospective, consecutive, non-randomized, comparative single-masked cohort study	2007-2011	2 mos	13	5 mos	Non-vision-threatening periocular IHs Various types	2 drops of 0.25% gel	BID	Timolol group 8 (62%): good response** 4 (31%): moderate response 1 (8%): poor response Observed group 0 (0%): good response 1 (10%): moderate response 9 (90%): poor response Timolol-treated superficial (n = 5; 100% good response) and mixed (n = 7; 43% good, 57% moderate response) IHs decreased in size; the one deep IH increased in size (poor response) despite topical timolol treatment.	None	1/13; no recurrence after re-initiation of treatment for an additional 6 mos.

Comments:

*= mean

†Blinded photo score = one blinded investigator scored clinical photographs based on IH redness (0 = no redness, 1 = ~50% red, and 2 = completely red).

VAS (Visual Analogue Scale) is a 100-mm scale (−100 = doubling in the size and extent of the IH, 0 = no change, and +100 = complete shrinkage). 5 mm is equivalent to a 10% change.

**Response to therapy was subdivided into good (>50% decrease in size), moderate (0–50% decrease in size), and poor (increased in size or led to visually significant ptosis or astigmatism).

Rebound growth was observed in only one patient: a 5-month-old infant with a mixed IH that almost completely resolved during a 2 month course of topical timolol but increased in size within 2 weeks of stopping treatment. Regression occurred with reintroduction of timolol, and rebound growth did not recur after treatment cessation at 1 year of age [12]. Sleep disturbance in one patient was the only reported adverse event from the 101 timolol-treated patients in the reviewed studies [11].

Conclusions

Beta blockers are currently the standard of care for IH. Oral propranolol has been the focus of most research and studies in treatment of IH. In December 2011, a multidisciplinary panel of experts established consensus recommendations (Figure 1) for propranolol pretreatment workup, initiation, formulation, target dose, frequency, and monitoring. According to these guidelines, pretreatment ECG should be obtained if heart rate is below normal for age, if the patient has a history of arrhythmia or current arrhythmia, if there is a family history of congenital heart conditions or arrhythmias, or if there is a maternal history of connective tissue disease.

The recommended formulation is 20mg/5mL preparation, and the recommended target dose is 1-3 mg/kg/day, with the majority of panel experts encouraging 2 mg/kg/day, divided into three daily doses [32]. Propranolol hydrochloride oral solution (Hemangeol®) is now FDA-approved for the treatment of proliferating IH with a concentration of 4.28 mg/ml and a recommended dose of 3.4 mg/kg/day divided into twice a day dosing [33]. A low starting dose is encouraged because most episodes of bradycardia and hypotension occur during initiation of treatment or dose escalation. Heart rate and blood pressure should be measured at baseline and 1 and 2 hours after the first propranolol dose and after dose escalations > 0.5 mg/kg/day. Also, a minimum of one set of vital signs should be measured when the patient reaches target dose. If heart rate or blood pressure

is abnormal for the patient's age, continue monitoring until they are within normal limits. Inpatient monitoring for initiation of oral propranolol is recommended for infants ≤ 8 weeks corrected gestational age, infants with poor social support, infants with cardiovascular or respiratory comorbidities, and infants who require maintenance of blood glucose. Otherwise, outpatient initiation of propranolol is acceptable [32].

Propranolol Treatment Consensus Recommendations	
Pretreatment ECG if	HR is below normal for age < 1 month old: < 70 bpm 1-12 months old: < 80 bpm >12 months old: < 70 bpm
	History of arrhythmia or current arrhythmia
	Family history of congenital heart conditions or arrhythmias
	Maternal history of connective tissue disease
Inpatient initiation if	≤ 8 weeks corrected gestational age
	Poor social support
	Cardiovascular or respiratory comorbidities
	Require maintenance of blood glucose
Formulation	20mg/5mL preparation
Target dose	1-3 mg/kg/d (majority recommend 2 mg/kg/d)
Frequency	TID
HR and BP monitoring at	Baseline
	1 and 2 hours after the first propranolol dose
	After dose escalations > 0.5 mg/kg/d
	Target dose

Figure 1. Propranolol treatment consensus recommendations

More recently, investigations of the efficacy and safety of other beta blockers have been conducted. Data from Ábarzúa-Araya et al. and de Graaf et al. show similar efficacy of propranolol and atenolol in treatment of IH, with atenolol having less side effects. Furthermore, since atenolol selectively antagonizes β 1-receptors and spares β 2-receptors, it is not contraindicated in patients with asthma or bronchial hyper-reactivity. Another advantage of atenolol is once daily administration which may improve compliance [8, 9]. More studies are recommended to strengthen the evidence of atenolol use in IH.

According to results from the cohort study by Pope et al., nadolol was faster and more effective than propranolol for inducing IH involution. In patients with proliferative IH, nadolol had a significantly better outcome when compared to propranolol. The longer half-life of nadolol allows twice daily dosing and may increase adherence [34]. More studies of nadolol efficacy in patients with IH are needed. To our knowledge, there are no randomized controlled trials of nadolol for treatment of IH.

Hydrophilic atenolol and nadolol cannot cross the blood brain barrier, theoretically reducing CNS adverse events, such as sleep disturbance, nightmares, and potential long-term memory loss. Of note, eight patients treated with atenolol had "transient restless sleep" [9], and one patient receiving nadolol suffered from "sleeping disturbance," [34] without further details provided.

Lastly, topical timolol is a good alternative to oral propranolol for smaller, more superficial IH [10, 11, 12]. Based on our review, topical timolol may have a slower onset of action compared to oral propranolol. In addition, topical timolol may be used as an

adjunct to shorten duration of oral therapy and to prevent rebound growth. Topical therapy may be beneficial for patients who have contraindications to systemic beta blockers or parents who are worried about the adverse effects of systemic therapy.

In conclusion, the superior safety and efficacy of propranolol over previously used corticosteroids is widely accepted. Currently, oral propranolol is first-line therapy for complicated IH. However, with the emerging use of other beta blockers for IH, we may see a shift in treatment recommendations in the coming years as more studies are published and the long term effects of beta-blocker use in infants continues to be evaluated.

References

1. Kilcline C, Frieden IJ. Infantile hemangiomas: How common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25(2):168-173. [PMID:18429772]
2. Kanada KN, Merin MR, Munden A, Friedlander SF. A prospective study of cutaneous findings in newborns in the united states: Correlation with race, ethnicity, and gestational status using updated classification and nomenclature. J Pediatr. 2012;161(2):240-245. [PMID:22497908]
3. Püttgen KB. Diagnosis and management of infantile hemangiomas. Pediatr Clin North Am. 2014;61(2):383-402. [PMID:24636652]
4. Dalby TK, Lester-Smith D. Propranolol for the treatment of infantile haemangioma. J Paediatr Child Health. 2013;49(2):148-151. [PMID:23418706]
5. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: A systematic review. Pediatr Dermatol. 2013;30(2):182-191. [PMID:23405852]
6. Léauté-Labrèze C, de lR, Hubiche T, Boralevi F, Thambo J, Taïeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649-2651. [PMID:18550886]
7. 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. [PMID:22762503]
8. Abarzúa-Araya Á, Navarrete-Dechent CP, Heusser F, Retamal J, Zegpi-Trueba MS. Atenolol versus propranolol for the treatment of infantile hemangiomas: A randomized controlled study. J Am Acad Dermatol. 2014;70(6):1045-1049. [PMID:24656727]
9. de Graaf M, Raphael MF, Breugem CC, et al. Treatment of infantile haemangiomas with atenolol: Comparison with a historical propranolol group. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2013;66(12):1732-1740. [PMID:24011909]
10. Chan H, McKay C, Adams S, Wargon O. RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. Pediatrics. 2013;131(6):e1739-e1747. [PMID:23650294]
11. 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. [PMID:22150436]
12. Chambers CB, Katowitz WR, Katowitz JA, Binenbaum G. A controlled study of topical 0.25% timolol maleate gel for the treatment of cutaneous infantile capillary hemangiomas. Ophthal Plast Reconstr Surg. 2012;28(2):103-106. [PMID:22410658]
13. Leaute-Labreze C, Dumas de la Roque E, Nacka F, et al. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants < 4 months of age. Br J Dermatol. 2013;169(1):181-183. [PMID:23301692]
14. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics. 2011;128(2):e259-66. [PMID:21788220]
15. Bauman NM, McCarter RJ, Guzzetta PC, et al. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas: A randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2014;140(4):323-330. [PMID:24526257]
16. 16. Malik MA, Menon P, Rao KL, Samujh R. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: A randomized controlled study. J Pediatr Surg. 2013;48(12):2453-2459. [PMID:24314186]
17. Sans V, de la Roque ED, Berge J, et al. Propranolol for severe infantile hemangiomas: Follow-up report. Pediatrics. 2009;124(3):e423-31. [PMID:19706583]
18. Vercellino N, Romanini MV, Pelegrini M, Rimini A, Occella C, Dalmonte P. The use of propranolol for complicated infantile hemangiomas. Int J Dermatol. 2013;52(9):1140-1146. [PMID:23829783]
19. Sondhi V, Patnaik SK. Propranolol for infantile hemangioma (PINCH): An open-label trial to assess the efficacy of propranolol for treating infantile hemangiomas and for determining the decline in heart rate to predict response to propranolol. J Pediatr Hematol Oncol. 2013;35(7):493-499. [PMID:23929318]
20. Ma X, Zhao T, Xiao Y, et al. Preliminary experience on treatment of infantile hemangioma with low-dose propranolol in china. Eur J Pediatr. 2013;172(5):653-659. [PMID:23340697]
21. Celik A, Tiryaki S, Musayev A, Kismali E, Levent E, Ergun O. Propranolol as the first-line therapy for infantile hemangiomas: Preliminary results of two centers. J Drugs Dermatol. 2012;11(7):808-811. [PMID:22777220]

22. Kagami S, Kuwano Y, Shibata S, et al. Propranolol is more effective than pulsed dye laser and cryosurgery for infantile hemangiomas. Eur J Pediatr. 2013;172(11):1521-1526. [PMID:23812512]
23. Holmes WJ, Mishra A, Gorst C, Liew SH. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. J Plast Reconstr Aesthet Surg. 2011;64(4):445-451. [PMID:20797926]
24. Corapcioglu F, Buyukkapu-Bay S, Binnetoglu K, Babaoglu A, Anik Y, Tugay M. Preliminary results of propranolol treatment for patients with infantile hemangioma. Turk J Pediatr. 2011;53(2):137-141. [PMID:21853649]
25. Talaat AA, Elbasiouny MS, Elgendy DS, Elwakil TF. Propranolol treatment of infantile hemangioma: Clinical and radiologic evaluations. J Pediatr Surg. 2012;47(4):707-714. [PMID:22498385]
26. 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. [PMID:21844428]
27. Saint-Jean M, Leaute-Labreze C, Mazereeuw-Hautier J, et al. Propranolol for treatment of ulcerated infantile hemangiomas. J Am Acad Dermatol. 2011;64(5):827-832. [PMID:21353332]
28. Hermans DJJ, van Beynum IM, Schultze Kool LJ, van de Kerkhof, Peter Cornelius Maria, Wijnen MHWA, van der Vleuten, Catharina Joanna Maria. Propranolol, a very promising treatment for ulceration in infantile hemangiomas: A study of 20 cases with matched historical controls. J Am Acad Dermatol. 2011;64(5):833-838. [PMID:21353329]
29. Buckmiller LM, Munson PD, Dyamenahalli U, Dai Y, Richter GT. Propranolol for infantile hemangiomas: Early experience at a tertiary vascular anomalies center. Laryngoscope. 2010;120(4):676-681. [PMID:20112413]
30. Manunza F, Syed S, Laguda B, et al. Propranolol for complicated infantile haemangiomas: A case series of 30 infants. Br J Dermatol. 2010;162(2):466-468. [PMID:20055816]
31. Fuchsmann C, Quintal MC, Giguere C, et al. Propranolol as first-line treatment of head and neck hemangiomas. Arch Otolaryngol Head Neck Surg. 2011;137(5):471-478. [PMID:21576558]
32. Bagazgoitia L, Torrelo A, Gutierrez JC, et al. Propranolol for infantile hemangiomas. Pediatr Dermatol. 2011;28(2):108-114. [PMID:21385205]
33. Zvulunov A, McCuaig C, Frieden IJ, et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: A multicenter retrospective study. Pediatr Dermatol. 2011;28(2):94-98. [PMID:21362031]
34. 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. [PMID:23266923]
35. Oral propranolol (hemangeol) for infantile hemangioma. The Medical Letter on Drugs and Therapeutics. 2014;56(1447):61-62. [PMID:25046418]
36. 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. [PMID:22762503]