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# Rebound Growth of Infantile Hemangiomas After Propranolol Therapy

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abstract

**BACKGROUND AND OBJECTIVES:** Propranolol is first-line therapy for problematic infantile hemangiomas (IHs). Rebound growth after propranolol discontinuation is noted in 19% to 25% of patients. Predictive factors for rebound are not completely understood and may alter the management approach. The goal of the study was to describe a cohort of patients with IHs treated with propranolol and to identify predictors for rebound growth.

**METHODS:** A multicenter retrospective cohort study was conducted in patients with IHs treated with propranolol. Patient demographic characteristics, IH characteristics, and specifics of propranolol therapy were obtained. Episodes of rebound growth were recorded. Patients' responses to propranolol were evaluated through a visual analog scale.

**RESULTS:** A total of 997 patients were enrolled. The incidence of rebound growth was 231 of 912 patients (25.3%). Mean age at initial rebound was 17.1 months. The odds of rebound among those who discontinued therapy at <9 months was 2.4 (odds ratio [OR]: 2.4; 95% confidence interval [CI]: 1.3 to 4.5;  $P = .004$ ) compared with those who discontinued therapy between 12 to 15 months of life. Female gender, location on head and neck, segmental pattern, and deep or mixed skin involvement were associated with rebound on univariate analysis. With multivariate analysis, only deep IHs (OR: 3.3; 95% CI: 1.9 to 6.0;  $P < .001$ ) and female gender (OR: 1.7; 95% CI: 1.1 to 2.6;  $P = .03$ ) were associated. Of those with rebound growth, 83% required therapeutic modification including 62% of patients with modifications in their propranolol therapy.

**CONCLUSIONS:** Rebound growth occurred in 25% of patients, requiring modification of systemic therapy in 15%. Predictive factors for rebound growth included age of discontinuation, deep IH component, and female gender. Patients with these predictive factors may require a prolonged course of therapy.



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Dr Shah contributed to the study design and the development of data collection instruments, coordinated enrollment of patients between all 10 sites, enrolled patients at 1 site, analyzed

**WHAT'S KNOWN ON THIS SUBJECT:** Propranolol is first-line therapy in the treatment of infantile hemangiomas. Rebound growth after discontinuation of treatment has been reported to be as high as 19% to 25%. Small retrospective reports document female gender and deep hemangiomas as conferring an increased risk of rebound growth.

**WHAT THIS STUDY ADDS:** This is the largest retrospective cohort study assessing rebound growth after propranolol therapy for infantile hemangioma. Several risk factors are associated with rebound growth, which may help to identify those infantile hemangiomas that may require prolonged treatment to avoid rebound growth.

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Infantile hemangiomas (IHs) are the most common childhood tumor, with an incidence of ~4%.<sup>1</sup> Their growth cycle is divided into early and late proliferative stages, followed by a slow involution phase.<sup>2-4</sup> Clinical characteristics of IH, such as morphology (ie, a prominent deep component), distribution (ie, segmental), size, and location are often indications for treatment to decrease the risk of functional impairment, ulceration, and permanent disfigurement.

Propranolol has become the first-line therapy for IHs that require treatment.<sup>5</sup> Although the exact mechanism of action is not known, propranolol may exert its effect on IH through several distinct pathways, including inhibition of angiogenesis or vasculogenesis, recruitment of endothelial progenitor cells to the IH site, vasoconstriction, and effects on cells within hemangiomas, including increased pericyte contractility and promotion of accelerated and dysregulated adipogenesis in IH stem cells.<sup>6-10</sup>

As experience with propranolol for IHs accumulates, there have been several reports of rebound growth after propranolol cessation, including at ages when IHs would not typically be expected to grow (eg, after 12 months).<sup>11-15</sup> The incidence of rebound is between 6% and 25%.<sup>16</sup> Predictive factors for rebound growth have not been completely elucidated. Identifying risk factors for rebound growth could affect treatment strategies, particularly duration of therapy. Therefore, the goals of this study were to describe a large cohort of patients with IHs who responded to propranolol therapy and to determine the incidence, characteristics of therapy, and predictive factors for rebound growth.

## METHODS

Patients with IHs treated with propranolol between 2008 and 2013

were retrospectively enrolled from pediatric dermatology and vascular anomalies centers, the majority of whom were from the Hemangioma Investigator Group. Inclusion criteria were (1) patients who completed therapy that had a course of at least 3 months on propranolol and (2) patients with ongoing therapy at the time of enrollment whose course of propranolol was at least 6 months. Exclusion criteria were as follows: (1) patients >3 years of age at time of propranolol initiation, (2) patients who were noncompliant with therapy, (3) insufficient patient follow-up, and (4) nonresponders to propranolol therapy. Overall, 10 sites enrolled patients from North America and Europe (Supplemental Table 6). Each site gained approval from its institutional review board to allow for participation.

With the use of the online data-capture program REDCap (Research Electronic Data Capture), a standardized questionnaire was created to identify the incidence of rebound growth of IHs treated with propranolol. Patient demographic characteristics, IH characteristics, previous therapy, and specifics of propranolol therapy were recorded. The presence of rebound growth was noted, along with its specific characteristics and any alterations in therapy as a result. In the literature, major rebound growth is defined as the need to alter systemic propranolol therapy (with either dose adjustment or reinitiation), whereas minor rebound is defined as those cases in which rebound was noted but no change or reinitiation of systemic therapy was necessary. These definitions were adopted as a clinically relevant outcome measure to categorize rebound growth.<sup>17</sup>

To assess overall response to propranolol, serial clinical images of all enrolled patients were reviewed by using a 100-mm visual analog scale (VAS), with a range of -100 to +100, where "0" represented

no change, "-100" represented doubling, and "+100" indicated complete resolution. VAS was a proxy measure of the IH percentage change (with negative values indicating proliferation and positive values representing involution). The VAS tool has been well described as a method for evaluating IH response to treatment in a variety of studies.<sup>18-21</sup>

Through REDCap, de-identified patient data were compiled and statistical analysis was performed at the University of California at San Francisco. Basic summary statistics were used to describe patient demographic characteristics, IH characteristics, specifics of propranolol therapy, and presence of rebound growth. Logistic regression was used to assess potential predictive factors for rebound growth. Odds ratios (ORs), corresponding 95% confidence intervals (CIs), and *P* values were calculated. Estimates of the probability of rebound for 8 common clinical scenarios were calculated by using the results of a multivariable logistic model. A mixed model that allowed person-specific random intercept, slope, and quadratic terms was used to model the trajectory of VAS over time. All statistical analyses were performed by using SAS software, version 9.4 (SAS Institute, Cary, NC).

## RESULTS

Details with regard to patient demographic characteristics, clinical characteristics of studied IHs, as well as specifics of propranolol therapy are summarized in Table 1.

### Demographic Characteristics

A total of 997 patients with IHs were enrolled from 10 academic centers between 2008 and 2013; however, 17 patients were excluded due to insufficient data, leaving a total of 980 for further analysis. Of these 980 patients, 225 (23.0%) were male and

**TABLE 1** Demographic Characteristics of Enrolled Patients, Distinguishing Clinical Features of Studied IHs, and Specifics of Propranolol Therapy

Feature	All (N = 980)	With Rebound Growth (n = 231)	No Rebound Growth (n = 749)	P
Demographic characteristics, n (%)				
Gender				.71 <sup>a</sup>
Male	225 (23.0)	38 (16.5)	187 (25.0)	
Female	753 (76.8)	193 (83.5)	560 (74.8)	
Missing	2 (0.2)	0 (0.0)	2 (0.3)	
Gestational age				.70 <sup>a</sup>
Term (37–42 weeks)	801 (81.7)	191 (82.7)	610 (81.4)	
Premature (<37 weeks)	178 (18.2)	40 (17.3)	138 (18.4)	
Missing	1 (0.1)	0 (0.0)	1 (0.1)	
Multiple gestation				.29 <sup>b</sup>
Yes	71 (7.2)	19 (8.2)	52 (6.9)	
No	851 (86.8)	194 (84.0)	657 (87.7)	
Unknown	58 (5.9)	18 (7.8)	40 (5.3)	
IH characteristics, n (%)				
Location				.005 <sup>b</sup>
Head and neck, localized	688 (70.2)	163 (70.6)	525 (70.1)	
Head and neck, segmental	134 (13.7)	43 (18.6)	91 (12.1)	
Body	158 (16.1)	25 (10.8)	133 (17.8)	
Morphology				<.001 <sup>b</sup>
Superficial	249 (25.4)	41 (17.7)	208 (27.8)	
Deep	188 (19.2)	62 (26.8)	126 (16.8)	
Combined	531 (54.2)	128 (55.4)	403 (53.8)	
Distribution				.034 <sup>b</sup>
Localized	776 (79.2)	170 (73.6)	606 (80.9)	
Segmental	174 (17.8)	52 (22.5)	122 (16.3)	
Indeterminate	26 (2.7)	9 (3.9)	17 (2.3)	
Size (surface area)				.15 <sup>b</sup>
0–10 cm <sup>2</sup>	535 (54.6)	129 (55.8)	406 (54.2)	
>10–50 cm <sup>2</sup>	228 (23.3)	47 (20.3)	181 (24.2)	
>50–100 cm <sup>2</sup>	56 (5.7)	16 (6.9)	40 (5.3)	
>100 cm <sup>2</sup>	35 (3.6)	13 (5.6)	22 (2.9)	
Missing	126 (12.9)	26 (11.3)	100 (13.4)	
Ulceration before therapy	182 (18.6)	44 (19.0)	138 (18.4)	.87 <sup>b</sup>
Propranolol therapy specifics				
Age at initiation, mean, <sup>c</sup> mo	5.64 ± 6.80	5.61 ± 6.93	5.64 ± 6.40	.71 <sup>a</sup>
Maximum dose of propranolol, mg/kg per day	1.95 ± 0.48	2.01 ± 0.48	1.94 ± 0.48	.21 <sup>a</sup>
Total duration of therapy, mean, <sup>d</sup> mo	11.96 ± 5.61	11.6 ± 6.77	10.8 ± 5.18	.55 <sup>a</sup>

±, Standard Deviation.

<sup>a</sup> Based on Mann-Whitney test.<sup>b</sup> Based on  $\chi^2$  test.<sup>c</sup> n = 228 and 739 for “With Rebound Growth” and “No Rebound Growth,” respectively.<sup>d</sup> n = 216 and 675 for “With Rebound Growth” and “No Rebound Growth,” respectively.

753 (76.8%) were female. A total of 801 (81.7%) patients were term and 178 (18.2%) were preterm infants (17% of girls and 22% of boys;  $P = .08$ ). Seventy-one (7.2%) patients were products of a multiple gestation (6% of girls and 1% of boys;  $P = .78$ ).

### Clinical Characteristics

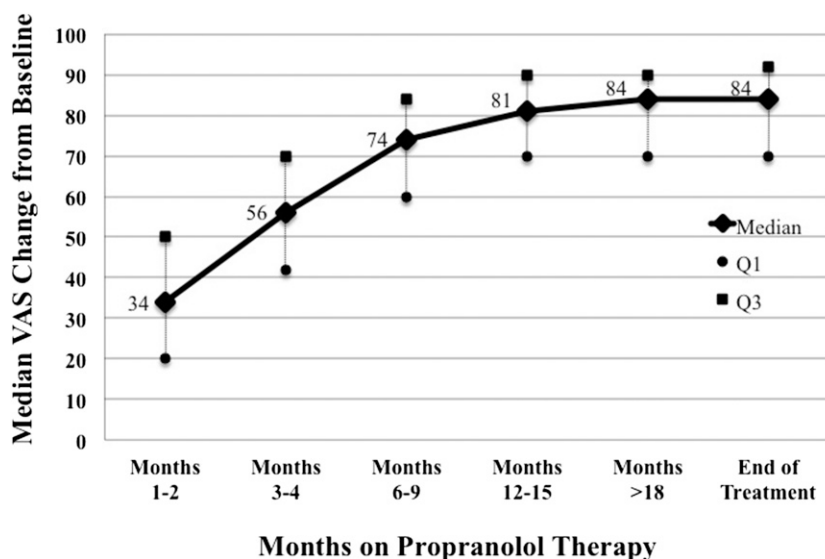
Of IHs, 83.9% were located on the head and neck, with 16.1% on other body sites. A total of 249 (25.4%) patients had superficial IHs, 188 (19.2%) had deep IHs, and 531 (54.2%) had combined

IHs (with both superficial and deep components). A total of 776 patients had localized hemangiomas (79.2%), 174 had segmental IHs (17.8%), and 26 patients had indeterminate IHs (2.7%). Of the segmental IHs, 38 (21.5%) had associated PHACE (Posterior fossa anomalies, Hemangioma, Arterial lesions, Cardiac abnormalities/aortic coarctation, Eye abnormalities) syndrome, 6 (3.4%) had probable PHACE syndrome, and 4 (2.3%) had LUMBAR (Lower body infantile hemangioma, Urogenital

anomalies/ulceration, Myelopathy, Bony deformities, Anorectal malformations/arterial anomalies, Rectal anomalies) syndrome. A total of 182 (18.6%) patients had ulceration before initiation of propranolol.

### Specifics of Propranolol Therapy: Indications, Dosage, and Discontinuation

A total of 643 (65.6%) patients were treatment naive before the initiation of propranolol. Of those who had received treatment, 182 (18.6%)



**FIGURE 1** Median VAS change after propranolol initiation. IH clinical response to propranolol was evaluated at specific time periods after the initiation of therapy (months 1–2, months 3–4, months 6–9, months 12–15, months >18, and end of treatment) through review of clinical photographs and the use of a 100-mm VAS, where –100 indicated doubling in size and +100 indicated complete resolution. Median percentage point improvements are noted for each time period. Vertical lines represent the IQR and the middle data point represents the median.

had local therapy only (defined as either timolol, topical or intralesional corticosteroids, localized wound care, pulsed-dye laser), 121 (12.4%) had systemic therapy (almost exclusively systemic corticosteroids), and 34 (3.5%) had previously received a combination of local and systemic therapy.

The risk of disfigurement was an indication for treatment in 68.1% of patients ( $n = 667$ ). In 400 patients (40.8%), therapy was indicated to address functional impairment and in 143 infants (14.6%) to treat ulceration (either alone or in combination with another indication).

The mean age at initiation of propranolol was  $5.6 \pm SD 6.8$  months, with a median of 4 months (interquartile range [IQR]: 2–6 months). A total of 453 patients (46.2%) were started on propranolol at  $\leq 3$  months of age. The mean maximum dose of propranolol was  $1.95 \pm SD 0.48$  mg/kg per day (range: 0.5–4 mg/kg per day). Of note, this dose range was nearly identical to that of those who experienced

rebound growth (0.76–4 mg/kg per day). Patients remained at their maximum dose for a mean duration of  $7.02 \pm SD 4.29$  months, with a mean total duration of  $12.0 \pm SD 5.6$  months. There was no difference in duration for those patients treated primarily for ulceration compared with those treated for other indications ( $P = .94$ ). Dosage adjustments for weight gain were performed in 70.8% of patients. Sixty-eight patients (9%) were still receiving the full dose of the medication at the time of the study. Excluding those receiving the full dose of propranolol, weaning of medication occurred in 794 patients (87%). Methods of weaning included “passive weaning” in which patients were allowed to outgrow their dose, which was seen in 235 of 794 (29.6%) patients, and “active weaning” in which doses were purposefully decreased, which was noted in 550 of 794 (69.3%) patients.

### Response to Propranolol

In assessing for response to propranolol, a VAS was used based

on serial patient photographs at various points during their treatment course. Within the first 1 to 2 months of receiving therapy, the median percentage improvement was 34% (IQR: 20%–50%). After 12 months, the median percentage improvement was 81% (IQR: 70%–90%); at the end of treatment there was a mean improvement of 84% (IQR: 70%–92%) (Fig 1).

VAS scores after 12 to 15 months of receiving therapy were compared by age of initiation (eg,  $\leq 3$  months, 3–6 months, and  $\geq 6$  months of age). Subjects whose propranolol was initiated at  $\leq 3$  months of age had a VAS score that was 6.0 (95% CI: 2.8 to 8.7;  $P < .001$ ) percentage points higher and subjects started on propranolol between ages 3 and 6 months had a VAS score that was 6.3 (95% CI: 3.1 to 9.5;  $P < .001$ ) percentage points higher than those who started propranolol  $\geq 6$  months of life. These 2 groups (those initiated on propranolol at  $\leq 3$  months of life and those between 3–6 months) had similar VAS scores with a difference of only 0.57 percentage points (95% CI: –2.1 to 3.3;  $P = .68$ ).

### Rebound Growth

The overall incidence of rebound growth was 25.3% (231 of 912 patients, excluding the 68 patients who were receiving the full dose of propranolol at the time of the study). Table 2 summarizes the specific details with regard to the timing, characteristics of rebound growth, as well as changes in management in response to rebound growth. A total of 174 patients discontinued therapy before the onset of rebound growth, with a median interval of 152 days (IQR: 66–222 days). Of the 231 patients with rebound growth, 191 (82.6%) required some type of therapeutic modification. Major rebound growth was noted in 143 of 231 patients (61.9%), with



minor rebound seen in 88 patients (38.1%).

### Predictive Factors for Rebound Growth

The mean duration of treatment before rebound growth was 11.4 months (median: 10 months; IQR: 7–14.5 months). The mean age at first episode of rebound growth was 17.1 months (median: 15 months; IQR: 11–21 months). Figure 2A summarizes the risk of rebound by age (reference category: 12–15 months) and Fig 2B shows the duration of therapy before the development of rebound. There was no association between age at discontinuation and amount of time that had lapsed after the first episode of rebound growth ( $P = .71$ ). Compared with those who discontinued propranolol between 12 and 15 months of age, the odds of rebound were highest for those who stopped propranolol before the age of 9 months (OR: 2.4; 95% CI: 1.3 to 4.5). The ORs (95% CI) of rebound were 2.0 (1.1 to 3.4;  $P = .02$ ), 1.7 (0.82 to 3.6;  $P = .15$ ), and 2.5 (1.5 to 4.3;  $P < .001$ ) when propranolol was discontinued between 18 and 21 months, at 21–24 months, and >24 months, respectively, when compared with the reference group. The higher risk of rebound growth in those >24 months is not completely clear. We believe that this finding represents a particular subset of problematic IHs that are larger in size and deep in morphology. This prolonged growth phase has previously been described in patients before propranolol was a treatment option.<sup>22</sup>

We further analyzed the group with rebound growth after 18 months of age ( $n = 92$ ) to see if they differed from those with rebound growth at earlier ages ( $n = 136$ ), excluding 3 patients with missing data. There were no statistical differences between these groups with respect to gender, gestational age, size, location

**TABLE 2** Rebound Growth Timing, Characteristics, and Therapeutic Response After Discontinuation or Tapering of Propranolol

Variable	Rebound Growth Cohort (N = 231)
Timing of rebound growth	
Duration between propranolol initiation and onset of rebound growth, mean, mo	11.4 ± 6.5
Age at initial episode of rebound growth, mean, median (IQR), mo	17.1 ± 8.7, 15 (11–21)
Patients with multiple episodes of rebound growth, <i>n</i>	40/231 (17.3)
Age at last episode of rebound growth, mean, mo	20.1 ± 10.1
Characteristics of rebound growth, <i>n/N</i> (%)	
Increase in volume	105/231 (45.5)
Increase in discoloration	36/231 (15.6)
Increase in volume and discoloration	64/231 (27.7)
Therapy modification for rebound growth, <i>n/N</i> (%)	
Major rebound (only systemic therapy modified)	143/231 (61.9)
Restart propranolol	75/143 (51.4)
Increase dose	49/143 (33.6)
Discontinue taper	21/143 (14.4)
Minor rebound (only local therapy modified)	88/231 (38.1)
Changes in local and systemic therapy	12/231 (5.2)

±, SD.

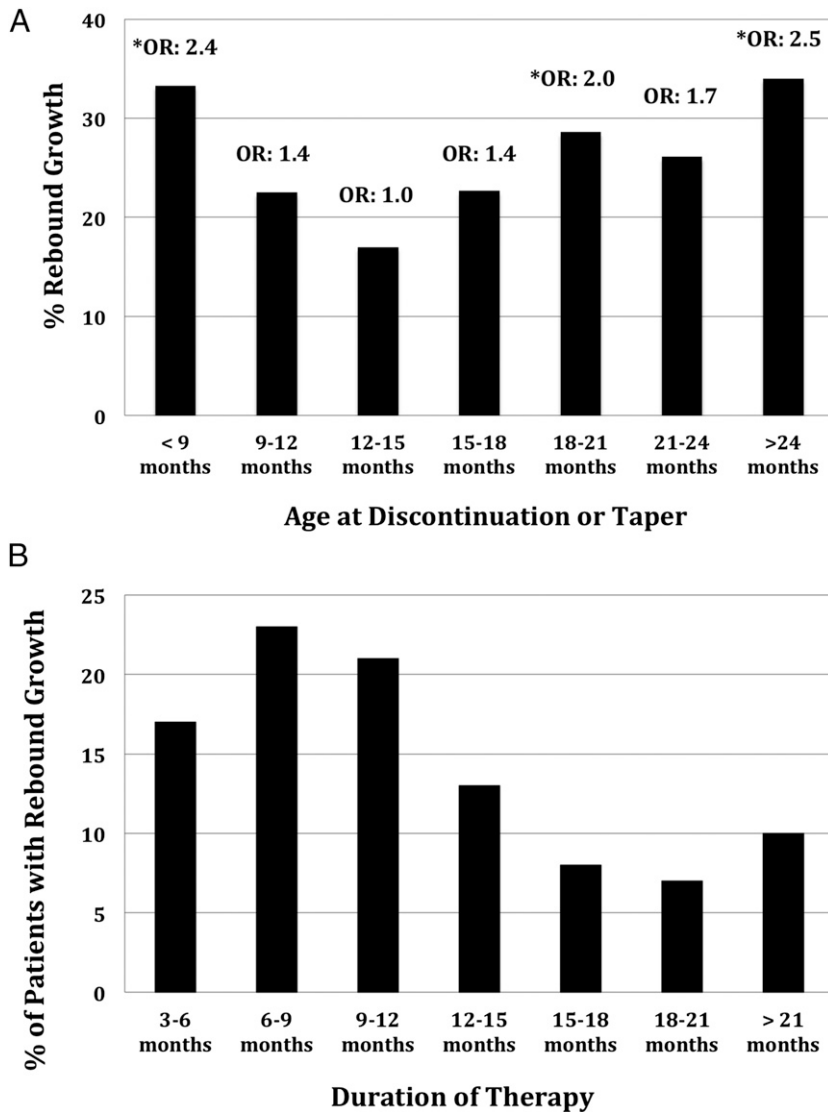
of IH, clinical characteristics, pattern, or method of discontinuation. Those who had rebound growth at age >18 months had a longer course of propranolol (mean: 12.8 ± SD 6.13 months) than did those with rebound before 18 months (mean: 10.8 ± SD 6.96;  $P = .002$ ). In addition, those who had rebound at age >18 months were more likely to be receiving higher maximum doses of propranolol compared with those who had early rebound ( $P < .001$ ).

Discontinuation of propranolol without tapering had a significantly increased risk of rebound growth by univariate analysis, although not in multivariate analysis ( $P = .37$ ). Of those patients who were tapered off the medication, 25.3% (148/586) developed rebound growth compared with 36.6% (41 of 112) who abruptly discontinued propranolol ( $P = .01$ ).

Predictive factors for rebound growth included head and neck location ( $P = .005$ ) and segmental distribution ( $P = .03$ ). Univariate analysis (Table 3) showed that segmental IHs were more likely to have rebound growth (OR: 1.5; 95% CI: 1.1 to 2.2;  $P = .03$ ) compared with localized IHs. Deep and mixed hemangiomas were more likely to

rebound (ORs: 2.5 [95% CI: 1.6 to 3.9;  $P < .001$ ] and 1.6 [95% CI: 1.1 to 2.4;  $P = .02$ ], respectively) compared with superficial IHs. Segmental IHs located on the head and neck were more likely to undergo rebound growth compared with localized hemangiomas on the body (OR: 2.5; 95% CI: 1.4 to 4.4;  $P = .001$ ). Univariate analysis revealed a gender difference, in that girls were more likely to develop rebound growth (OR: 1.7; 95% CI: 1.2 to 2.5;  $P = .007$ ).

Multivariate analysis (Table 4) confirmed that deep hemangiomas were 3.3 times more likely to develop rebound growth (OR: 3.3; 95% CI: 1.9 to 6.0;  $P < .001$ ) compared with superficial IHs, and combined or mixed hemangiomas with both superficial and deep components were 2.4 times more likely to develop rebound growth (OR: 2.4; 95% CI: 1.5 to 4.0;  $P < .001$ ). Girls were 1.7 times more likely to develop rebound growth (OR: 1.7; 95% CI: 1.1 to 2.6;  $P = .03$ ). Other factors such as size, segmental distribution, location, and duration of therapy were no longer statistically significant. A multivariable logistic model for rebound with predictors including gender ( $P = .02$ ), IH size ( $P = .03$ ), and morphology ( $P < .001$ ) was used to



**FIGURE 2**  
 A, Rebound risk by age at discontinuation or tapering of propranolol. By using months 12 to 15 as a reference range, the risk of rebound growth of IHs according to age at discontinuation was calculated by using logistic regression models. ORs represent the odds of rebound growth for each age category compared with the reference category. The greatest risk of rebound growth occurred in patients whose propranolol was discontinued before 9 months of life (OR: 2.4) or in those who were continued on the medication past 18 months of life. \* $P < .05$ . B, Duration of therapy before rebound growth. The percentage of patients who experienced rebound growth of IHs after discontinuation or tapering of propranolol therapy was calculated on the basis of duration of therapy. Patients with shorter courses of propranolol therapy experienced a higher percentage of rebound growth.

estimate the probabilities of rebound for 8 common clinical scenarios (Table 5).

## DISCUSSION

This study, which, to our knowledge, is the largest to date studying rebound growth, shows that rebound growth is relatively common but

may not always require changes in systemic therapy. Table 5 outlines common clinical scenarios noted with IHs including gender, morphology, and size of hemangiomas and their associated risk of rebound growth. These findings should help clinicians in determining which patients may require prolonged therapy to minimize rebound growth and help

to offer appropriate counseling and expected course for patients and families.

Among the most important findings was that patients whose propranolol therapy was discontinued before 9 months of age had a more than twofold increased risk of rebound growth. Those who continued propranolol until 12 to 18 months of life had the least risk of developing rebound growth. The most potent risk factor for rebound was the presence of a deep IH component (ie, deep or mixed morphology), which was also noted in other studies. Shehata et al<sup>14</sup> observed that 13 of 212 patients had documented late rebound growth, all of which was noted in either deep or mixed lesions. Agoho et al<sup>17</sup> also found that deep hemangiomas were 22 times more likely to develop rebound growth (OR: 22.40;  $P < .001$ ), likely because deep hemangiomas have a prolonged growth phase as compared with superficial IHs.<sup>2</sup>

Female gender conferred an increased risk of rebound growth in both univariate and multivariate analysis, confirming findings of 2 other reports. In a study by Bagazgoitia et al,<sup>13</sup> all 5 of 26 patients who experienced rebound growth of IH were girls. Ahogo et al<sup>17</sup> found that girls were at higher risk of rebound growth on univariate analysis (OR: 2.91;  $P < .01$ ) but not with multivariate analysis. The authors hypothesized that this finding likely resulted from girls having a higher risk of segmental hemangiomas. In contrast, our study found that girls were 1.7 times more likely to develop rebound growth, even after adjusting for other variables, further implicating gender as playing a role in rebound growth. The exact reasons for this are uncertain, but it appears that girls are intrinsically more predisposed not only to hemangioma development but also to growth.

Propranolol is still a relatively new medication for IH and questions remain regarding optimal dosing,



**TABLE 3** Univariate Logistic Regression for Rebound Risk After Discontinuation or Tapering of Propranolol

Variable	OR	Lower 95% CI	Upper 95% CI	<i>P</i>	Type 3 <i>P</i>
Gender					
Male	1.00				
Female	1.70	1.15	2.5	.007	
Location					
Body	1.00				
Head and neck, localized	1.65	1.04	2.6	.03	.005
Head and neck, segmental	2.5	1.44	4.4	.001	
Morphology					
Superficial	1.00				
Deep	2.5	1.59	3.9	<.001	.004
Combined/mixed	1.611	1.09	2.4	.016	
Distribution					
Localized	1.00				
Indeterminate	1.89	0.83	4.3	.13	
Segmental	1.52	1.05	2.2	.025	.035

duration of therapy, and methods for discontinuation. Our study found no statistical significance in rebound growth between differences in maximum dosing. However, the majority of patients were treated in the range of 1.5–2.5 mg/kg per day and therefore we cannot fully conclude whether there is any added protective or negative effect with higher doses. Tapering propranolol, whether through active or passive weaning, resulted in a lower incidence of rebound growth compared with abrupt discontinuation ( $P = .01$ ), which is important to note despite lack of significance on multivariate analysis.

The size of the cohort and details of the study allowed us to quantify the incidence of rebound growth, the nature of rebound, and need for further treatment. Sixty-two percent of those who experienced relapse had major rebound growth. However, in viewing the entire cohort, the percentage of patients with major rebound growth was 15.7% (143 of 912). On the basis of this finding, we can conclude that the large majority of patients do well upon tapering or discontinuation of the medication without need for further systemic treatment. Minor rebound growth was noted in 38.1% (88 of 231) of rebound patients and was typically managed with local therapies, such

**TABLE 4** Multivariate Logistic Regression for Rebound Risk After Discontinuation or Tapering of Propranolol

Variable	OR	Lower 95% CI	Upper 95% CI	<i>P</i>	Type 3 <i>P</i>
Gender					
Male	1.00				
Female	1.67	1.06	2.6	.03	
Location					
Body	1.00				
Head and neck	1.00				
Segmental	1.66	0.55	5.0	.37	
Head and neck	1.46	0.77	2.8	.25	
Localized					
Morphology					
Superficial	1.00				
Deep	3.3	1.87	6.0	<.001	<.001
Combined/mixed	2.4	1.50	4.0	<.001	
Distribution					
Localized	1.00				
Segmental	1.32	0.44	4.0	.62	
Indeterminate	1.45	0.53	4.0	.47	

Data were adjusted for total months of therapy, maximum dose, gestational age, multiple gestation, age at initiation of propranolol, size, functional airway impairment, and previous therapy type.

**TABLE 5** Common Clinical Scenarios for IHs and Associated Rebound Risk After Discontinuation or Tapering of Propranolol

Variable	Probability of Rebound	Lower 95% CI	Upper 95% CI
Male patients			
Superficial, <50 cm <sup>2</sup>	0.09	0.06	0.15
Mixed/deep, <50 cm <sup>2</sup>	0.20	0.14	0.26
Superficial, >50 cm <sup>2</sup>	0.15	0.09	0.25
Mixed/deep, >50 cm <sup>2</sup>	0.30	0.19	0.43
Female patients			
Superficial, <50 cm <sup>2</sup>	0.15	0.10	0.20
Mixed/deep, <50 cm <sup>2</sup>	0.29	0.25	0.33
Superficial, >50 cm <sup>2</sup>	0.23	0.15	0.33
Mixed/deep, >50 cm <sup>2</sup>	0.41	0.30	0.53

Common clinical scenarios including gender, hemangioma morphology, and size are shown with their associated probability of hemangioma rebound growth upon discontinuation or tapering of propranolol therapy. These common scenarios can be used by practitioners to understand which hemangiomas may be at greater risk of rebound growth and can aid in patient/parent education with regard to rebound risk and potentially expected duration of therapy.

as topical timolol, pulsed-dye laser, or intralesional steroids. This finding emphasizes the need for multimodal approaches, depending on clinical circumstances.

Our study also corroborates the efficacy of propranolol, evidenced by VAS scoring during therapy, with a mean improvement of 84% at the end of treatment. Due to the retrospective nature of the study, data on adverse events or safety were not collected.

The natural history of untreated IHs has been well established, including growth cessation typically occurring by 9 months of age, with a majority of hemangiomas completing growth by 5 months of age.<sup>2</sup> Prolonged growth may be seen in larger IHs with deep or segmental morphologies.<sup>22</sup> Propranolol reduces IH stem cell growth but does not produce true apoptosis of these cells.<sup>8,23</sup> It is plausible to assume that at least some IHs treated with propranolol undergo alterations in their natural history. Speculatively, discontinuation of propranolol could spur delayed growth due to the growth potential of IH stem cells that are still present.

There is now a Food and Drug Administration- and European Medicines Agency-approved medical therapy for IH, HEMANGEOL (Pierre Fabre Pharmaceuticals, Inc., Parsippany, New Jersey). The pivotal

study leading to approval for this medication showed that treatment of 6 months was more effective than for 3 months; however, the study design did not extend beyond 6 months.<sup>16</sup> Our study, albeit retrospective, shows that treatment of far longer duration may be necessary in a minority of patients. The mean total duration of treatment was 11 months in the entire cohort, and many infants experienced rebound after treatment of longer durations, with 10% having rebound growth after durations of treatment of  $\geq 18$  months.

A potential limitation of the study is that the patients enrolled represent a referral bias of more significant IHs requiring systemic therapy. It is widely appreciated that the majority of IHs do not require systemic treatment. It is also possible that, in some centers, IHs treated with systemic therapy may have a lesser degree of functional or cosmetic concern and, if so, propranolol dosing and duration and risk of rebound growth may also be less. Further studies may be beneficial to elucidate these questions.

## CONCLUSIONS

The goal of our study was to identify risk factors associated with rebound growth of IHs upon discontinuation or tapering of propranolol.

Understanding key risk factors for rebound growth such as IH depth and female gender may help guide decisions regarding the duration of systemic therapy and strategies for managing rebound growth. The information obtained from this study underscores the need to individualize treatment depending on indications for treatment, response to treatment, and risk factors for rebound growth.

Many unanswered questions remain, including whether different dosing regimens might be beneficial for those at greatest risk of rebound and the role of adjunctive therapies in minimizing regrowth. These questions may help to guide future directions for research.

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## ABBREVIATIONS

CI: confidence interval  
EMA: European Medicines Agency  
FDA: Food and Drug Administration  
IH: infantile hemangioma  
IQR: interquartile range  
OR: odds ratio  
VAS: visual analog scale

data, and drafted, reviewed, and revised the manuscript; Dr Baselga conceptualized and designed the study, contributed to the development of data collection instruments, supervised enrollment of patients at 1 site, and critically reviewed and revised the manuscript; Drs McCuaig and Pope contributed to the study design and the development of data collection instruments, supervised enrollment of patients at 1 site, and critically reviewed and revised the manuscript; Dr Coulie enrolled patients at 1 site and reviewed and revised the manuscript; Drs Boon, Garzon, Haggstrom, Adams, Drolet, and Newell supervised enrollment of patients at 1 site each and critically reviewed and revised the manuscript; Drs Powell, Garcia-Romero, Roe, and Siegel and Ms Chute enrolled patients at 1 site each and reviewed and revised the manuscript; Dr Grimes carried out all statistical analyses and reviewed and revised the manuscript; Dr Frieden contributed to the study design and development of data acquisition tools, analyzed data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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