Objectives: To report the efficacy of propranolol as first-line treatment of head and neck hemangiomas in children and to present an optimized protocol for treating hemangiomas.

Design: Multi-institutional retrospective study.

Setting: Two tertiary care referral pediatric centers.

Patients: Thirty-nine children with head and neck infantile hemangiomas were treated.

Main Outcome Measures: Review of clinical records.

Results: Propranolol was the sole treatment in 60% of patients and was started at a mean age of 4.1 months (age range, 1-11 months) for early interventions among 33 of 39 patients. Propranolol therapy resulted in lightening and reduction of hemangiomas at 37 of 39 locations within 2 days to 2 weeks. One subglottic hemangioma and 1 nasal tip hemangioma did not respond or showed only a partial response; in these patients, propranolol therapy was delayed and followed other treatment failures. After successful therapeutic regression, 6 recurrences occurred; when reintroduced, propranolol was again effective. Recurrences were avoided by prolonged treatment. Twenty-six hemangiomas occurring at locations for which corticosteroid treatment previously would not have been initiated (nose, lips, and parotid area) unless a complication had occurred were treated with propranolol and were rapidly controlled. The mean duration of propranolol therapy was 8.5 months. No instances of β-blocker discontinuation because of complications occurred, but propranolol was substituted by acebutolol in 5 patients because of trouble sleeping.

Conclusions: Propranolol is an effective treatment of head and neck infantile hemangiomas, especially when started early within the rapid growth phase, and is first-line treatment of orbit and larynx hemangiomas. The efficacy and tolerability of propranolol led us to treat some hemangiomas in patients whom we previously would have observed rather than subject to corticosteroid therapy. Relapse was avoided if treatment was prolonged after theoretical involution (age 12 months). Questions remain about optimal dosing and age at treatment cessation.


Infantile hemangiomas are the most common tumors of infancy, characterized by rapid endothelial proliferation shortly after birth. They affect approximately 4% to 10% of full-term infants of white race/ethnicity and are associated with prematurity, female sex, and low birth weight. Infantile hemangiomas appear within the first 2 months of life, and growth continues for the first 8 to 12 months. The lesion then enters an involutive phase, followed by more or less complete regression. Fifty percent of lesions are involuted by the time the child is age 5 years and 70% by age 7 years. Scars or fibrous fatty tissue can remain after lesion involution. Infantile hemangiomas can manifest a broad spectrum of clinical features ranging from small asymptomatic benign lesions to large function-threatening or life-threatening tumors. When located in the subglottis, they can cause life-threatening airway compromise; at other locations (periorificial or intraorbital) or in the event of ulceration, hemangiomas can cause important functional or cosmetic impairment. Therefore, treatment is required in these cases.

Until 3 years ago, the mainstay of treatment was oral corticosteroids, which are associated with well-known serious adverse effects, including growth disturbance, Cushing syndrome, diabetes mellitus, arterial hypertension, avascular necrosis of the hip, compromised immunity, and infec-
tious risk.1−4 In the case of extensive life-threatening corticosteroid-resistant hemangiomas, interferon alfa or vincristine sulfate is used, despite significant toxic effects.5−7

The efficacy of propranolol in the treatment of infantile hemangiomas was initially discovered by Leauté-Labrèze et al8 in 2 children who showed rapid regression of hemangiomas when treated for cardiopulmonary conditions. After this observation, several teams began to use β-blockers in children with hemangiomas. We report herein the outcomes of 39 children treated for head and neck infantile hemangiomas with β-blockers at 2 tertiary care referral pediatric centers.

METHODS

PATIENTS

Thirty-nine children with head and neck infantile hemangiomas were included in this multi-institutional retrospective study between January 10, 2008, and September 30, 2009, at 2 tertiary care referral pediatric centers (Hôpital Femme Mère Enfant, Bron, France, and Hôpital Sainte Justine, Montréal, Québec, Canada). None of these patients have been described in a prior publication. Treatment was considered because their hemangiomas were associated with local complications (ulceration), risk of functional or aesthetic impairment, or life-threatening locations (airway compromise or failure to thrive). At treatment onset, some children had already undergone previous therapy (surgery, prednisone, or local injection of corticosteroids).

The following variables were assessed: relapse, adverse effects, treatment duration, hemangioma location, age at treatment onset, and short-term and long-term clinical improvement. This study was approved by the institutional review boards of the 2 pediatric centers, and informed consent was obtained from both parents of the children.

TREATMENT PROTOCOL

Propranolol was prescribed to 39 children. After 1 month of treatment, acebutolol was substituted in 5 children because of trouble sleeping that was attributed to propranolol use.

Hemangioma assessment before treatment included clinical examination, photographs, and echographic evaluation (when possible) with measurement of vascular activity and maximal thickness of the lesion. In the case of orbital involvement, patients were examined by an ophthalmologist. For children with airway compromise due to a subglottic hemangioma, diagnosis was confirmed by airway endoscopic examination using general anesthesia.
Children had a pediatric cardiology consultation with electrocardiographic and echocardiographic evaluation to rule out treatment contraindications. The pediatric cardiologists agreed with the treatment plan to follow up clinical symptoms, as they do with their patients who are prescribed propranolol for cardiologic indications.

Baseline vital signs (pulse and blood pressure) were obtained before initiating treatment. Measurement of baseline blood glucose level was not obtained as part of our study.

Propranolol was started at 0.5 mg/kg/d in 3 divided doses for 2 days. Treatment was begun in an outpatient clinic with 2-hour follow-up or during a 1-day hospital session. Propranolol was increased to 1 mg/kg/d for 2 days and then 1 mg/kg every 48 hours to reach a dosage of 2 to 3 mg/kg/d. Treatment tolerance was monitored by the pediatrician after each increase.

The propranolol dosage was maintained at 2 mg/kg/d if a significant response was observed. Child age did not influence treatment initiation recommendations. Children with subglottic hemangiomas were hospitalized because of their dyspnea. Treatment tolerance was monitored by measuring pulse rate and blood pressure 1 hour after administration the first day and after each dosage increase. Parents were advised to stop treatment in the case of fasting because of hypoglycemia risk. They were also informed about the clinical signs of hypotension, bradycardia, hypoglycemia, asthmatic bronchitis, and sleep disturbances.

TREATMENT EVALUATION

After treatment onset, follow-up and assessment depended on the location and severity of the initial hemangioma. For patients with subglottic hemangiomas and dyspnea, an endoscopic evaluation using general anesthesia was performed 1 and 5 weeks after treatment onset. The other children were reevaluated 2 weeks after treatment onset and then every month by clinical evaluation. Sixteen children also underwent ultrasonographic evaluation, but it was not mandatory. Evaluation of propranolol efficacy was subjective, representing a clinical assessment of the hemangioma by 1 reviewer (C.F., M.-C.Q., L.G., or P.F.) based mainly on change in lesion size, with color and local health also assessed. Parents were asked to send photographs of their child 4 days after treatment onset. Efficacy was evaluated clinically as a rapid change in color after treatment introduction.

RESULTS

PATIENTS

Thirty-nine children, 27 female (ratio of boys to girls, 1:2.25), benefited from β-blocker treatment of infantile hemangiomas. None of these patients were described in a prior publication. Thirty-three children were younger than 1 year (mean age, 4.1 months; age range, 1-11 months) and benefited from early treatment. The mean age of the remaining 6 patients was 28.6 months (age range, 13-56 months). All patients underwent echocardiography before treatment, with 38 demonstrating normal results. One child had an atrial septal defect.

HEMANGIOMA LOCATIONS

Eight children had airway hemangiomas causing life-threatening obstruction or respiratory difficulties and failure to thrive. Five were obstructive subglottic hemangiomas (Figure 1), and 3 were hemangiomas causing nasal obstruction. Thirteen children had hemangiomas demonstrating risk of functional complications. These included a periocular location in 4 patients (eyelids or internal canthus) and an intraorbital location in 1 patient, with risk of amblyopia, astigmatism, or lacrimal duct obstruction. Six children had lip hemangiomas causing scars, painful ulcerations, or sucking difficulties. Two children had painful ulcerated intraoral hemangiomas. The remaining children had nasal tip (n=13) or facial (n=5) hemangiomas. Typical results are shown in Figures 2, 3, 4, and 5.

Figure 3. Three-month-old patient with a large nasal tip hemangioma. A and B, Initial views. C, Improvement after 3 months of propranolol treatment. D, Further improvement after 6 months of treatment.

Figure 4. Three-month-old patient with a nasal tip hemangioma. A, Initial view. B, Improvement after 2 months of propranolol treatment.
PREVIOUS TREATMENTS

Among 39 children, 16 had undergone previous treatment that was ineffective or could not be stopped without relapse. Nine patients had intralesional injection of corticosteroids, with no effect in 8 patients and stabilization in 1 patient. These injections were stopped before beginning propranolol treatment, as they seemed useless. General corticosteroids were prescribed to 7 children for at least 1 month, with no effect in 3 and hemangioma reduction or stabilization in 4. However, long-term corticosteroid treatment had many adverse effects, requiring discontinuation, which was followed by relapse. In 3 children with airway hemangiomas, prednisone was administered for 8 days during the acute phase to control dyspnea. Two patients with subglottic hemangiomas previously had benefited from laser treatments and corticosteroid injections, 1 of whom had undergone tracheotomy at another center (Table).

TREATMENT EFFICACY AND DURATION

Propranolol treatment was effective at 37 of 39 hemangioma locations within 2 days to 2 weeks. Spectacular improvement was noted within the first week of treatment in 14 patients before the target dosage was obtained. For 4 patients with subglottic hemangiomas, treatment resulted in regression and disappearance of their dyspnea, ability to feed orally within 1 week, and discharge home after 10 days. This response was obtained with combination therapy (propranolol and a short course of corticosteroids) in 3 children. One child with a circumferential hemangioma had already undergone laser debulking, local corticosteroid injections, and systemic corticosteroids, all of which had proved to be ineffective. Endoscopic evaluation of these 4 children after 5 weeks showed 80% regression of the lesions (Figure 1). Hemangiomas at other locations responded dramatically to β-blockers with a color change, lesion softening, and healing of ulcerations within the first 2 weeks of treatment. One subglottic hemangioma and 1 nasal tip hemangioma did not respond or showed only a partial response; in these patients, propranolol therapy had been started after several months of growth, at ages 13 and 14 months.

Ultrasonographic examination was performed in 16 patients. Results showed substantial decreases in he-
For early interventions, propranolol therapy was discontinued in 25 patients at ages ranging from 7 to 17 months (mean age, 12.5 months) after a mean treatment duration of 8.5 months (range, 2-14 months). No relapse was observed in 17 patients (treatment was stopped at a mean of 12.5 months), and mild regrowth or recoloration was noted in 3 patients at 7, 9, and 12 months after a mean of 5.0 months of treatment but did not require re-treatment. After successful therapeutic regression, recurrences occurred in 6 children; when reintroduced, propranolol was again effective. These children had a mean treatment duration of 5.2 months before stopping at a mean age of 9.5 months (age range, 7-11 months). Eight children are still under treatment.

For late interventions, propranolol treatment was effective in 4 of 6 patients. In these patients, ultrasonography showed continuation of substantial vascular activity.

There were no instances of β-blocker discontinuation because of complications, but propranolol was substituted by acebutolol in 5 children because of sleep disturbances (nights and frequent awakenings), which subsequently subsided. Two children had mild diarrhea within the first month of treatment. No cardiac adverse effect was reported. Blood glucose levels were checked in 22 patients before treatment and were normal. No clinical symptom related to hypoglycemia was observed. No difference in efficacy was observed between acebutolol and propranolol.

Since the fortuitous discovery of the efficacy of propranolol in treating infantile hemangiomas by the French team led by Léauté-Labrèze, several groups began to use this therapy and have reported excellent results. With in-

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creased experience, propranolol has become our first-line treatment of head and neck hemangiomas.

Like other research groups, we have been impressed by the remarkable efficacy of β-blockers and the rapidity of their effect on hemangiomas. Among 39 children treated with propranolol or acebutolol, 37 responded dramatically within the first 2 weeks regardless of the location of their hemangioma. Improvement was not only in the size but also in the quality of the lesion, which flattened and changed color. This was particularly notable in skin lesions that were directly accessible to clinical examination without ultrasonographic assessment. In 8 patients with painful ulcerative hemangiomas described by Michel and Patural, cutaneous or mucosal healing was observed shortly after initiation of treatment with propranolol. The improvement was corroborated by ultrasonography, which showed decreased vascular activity. Propranolol dosages of 2 mg/kg/d were sufficient to have a maximal effect on hemangiomas in 14 of 39 children and can be increased to 3 mg/kg/d. Optimal dosing and dose-related efficiency remain to be determined. In our series, relapses with the need to reintroduce treatment occurred when therapy was stopped at a mean age of 9.5 months. Individual variability in the natural history of hemangiomas must be considered, which makes it difficult to determine the age at which treatment may be discontinued. Ultrasonography monitors vascular activity within hemangiomas and, in conjunction with clinical observation, may indicate when propranolol can be stopped. Propranolol dosages of 2 mg/kg/d were sufficient to have a maximal effect on hemangiomas in 14 of 39 children and can be increased to 3 mg/kg/d. Optimal dosing and dose-related efficiency remain to be determined. In our series, 5 children treated with acebutolol showed the same response as others treated with pro-

### Table. Clinical Characteristics of 39 Children, Including Prior Treatment, β-Blocker Dosages and Duration, and Treatment Results (continued)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Location of Hemangioma</th>
<th>Indication for Treatment</th>
<th>Prior Treatment</th>
<th>Age at Treatment Disappearance, mo</th>
<th>Propranolol or Acebutolol Dosage, mg/kg/d</th>
<th>Treatment Duration, mo</th>
<th>Relapse After β-Blocker Treatment</th>
<th>Uteration Disappearance as a Result of Treatment, %</th>
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<tbody>
<tr>
<td>20</td>
<td>Upper lip</td>
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<td>Prednisone for 7 mo, relapse</td>
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<td>Lower lip</td>
<td>Painful ulceration, cosmetic risk</td>
<td>Intraliesional injection, worsening ulceration</td>
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<td>3</td>
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<tr>
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<td>Intralesional injection, no effect</td>
<td>13</td>
<td>3</td>
<td>2 No</td>
<td>Regrowth when stopped at 10 mo</td>
<td>50</td>
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<td>None</td>
<td>15</td>
<td>3</td>
<td>2 No</td>
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<td>Treatment is ongoing</td>
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<td>5</td>
<td>3</td>
<td>15 No</td>
<td>Regrowth when stopped at 10 mo</td>
<td>70</td>
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<tr>
<td>28</td>
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<td>Cosmetic risk</td>
<td>Intraliesional injection, local corticosteroid cream, stabilization</td>
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<td>Regrowth when stopped at 11 mo</td>
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<td>Cosmetic risk</td>
<td>Intraliesional injection, no effect</td>
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<td>3</td>
<td>4 Ongoing</td>
<td>Treatment is ongoing</td>
<td>50</td>
</tr>
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<td>3</td>
<td>5 Ongoing</td>
<td>Treatment is ongoing</td>
<td>75</td>
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<td>Cosmetic risk</td>
<td>Intraliesional injection, no effect</td>
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<td>3</td>
<td>5 No</td>
<td>No</td>
<td>75</td>
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<td>Cosmetic risk</td>
<td>Intraliesional injection, no effect</td>
<td>2</td>
<td>3</td>
<td>5 No</td>
<td>No</td>
<td>75</td>
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<td>Cosmetic risk</td>
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<td>3</td>
<td>9 No</td>
<td>Regrowth when stopped at 7 mo</td>
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<td>33</td>
<td>3</td>
<td>10 No</td>
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</table>

*Acebutolol dosage. All others are propranolol dosages.*

Given the natural history of hemangiomas, our findings, and those of others, β-blockers should be administered during the entire proliferative phase, which can last until age 7 to 12 months. An optimal duration of treatment is rarely reported; in many cases, propranolol therapy is ongoing. Relapse is observed in patients when treatment is stopped before age 1 year. In the study by Sans et al., relapses occurred after treatment cessation before age 11 months. Denoyelle et al. treated their patient with a laryngeal hemangioma until age 18 months, and no relapse was seen after cessation of propranolol. In our series, relapses with the need to reintroduce treatment occurred when therapy was stopped at a mean age of 9.5 months. Individual variability in the natural history of hemangiomas must be considered, which makes it difficult to determine the age at which treatment may be discontinued. Ultrasonography monitors vascular activity within hemangiomas and, in conjunction with clinical observation, may indicate when propranolol can be stopped. Propranolol dosages of 2 mg/kg/d were sufficient to have a maximal effect on hemangiomas in 14 of 39 children and can be increased to 3 mg/kg/d. Optimal dosing and dose-related efficiency remain to be determined. In our series, 5 children treated with acebutolol showed the same response as others treated with pro-

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propranolol. Bigorre et al\textsuperscript{13} previously described the efficacy of acebutolol in 2 patients with infantile hemangiomas. These findings should be confirmed in larger studies, as acebutolol is a cardioselective β-blocker. Indeed, unlike propranolol, which has selectivity to β1 and β2 receptors, acebutolol is selective only to β1 receptors. The proportions of β1 and β2 receptors vary among tissues. In the heart, most are β1 receptors, whereas β2 receptors predominate in the bronchi and vessels.

Propranolol was effective even when treatment was delayed after age 1 year. Hemangiomas in 4 of these 6 children responded quickly to propranolol therapy. Ultrasoundography before treatment had shown substantial residual vascular activity. The 2 late treatments that resulted in no response or only a partial response were in a patient with a subglottic hemangioma, tracheomalacia, and secondary stenosis related to the hemangioma and in a patient with a nasal tip hemangioma that had significant fibrous fatty tissue involution on ultrasoundography. Sans et al\textsuperscript{12} also report effective late intervention with propranolol in patients with infantile hemangiomas. These results need to be confirmed by other late treatments but are encouraging.

Among 13 patients herein with nasal tip hemangiomas that likely previously would have been surgically treated because of cosmetic risk and adverse effects of corticosteroids, only 1 patient required late surgery. Propranolol treatment seemed to limit the extension and reduce the hemangioma volume, leaving less remaining fibrous fatty tissue or none. Therefore, no early surgical resection was required. Among 4 patients with periorbital (eyelid) hemangioma locations, β-blocker treatment prevented amblyopia or astigmatism, without the need of corticosteroid treatment. One patient without functional complications will benefit from surgical excision of a small amount residual fibrous fatty tissue. In the patient having an intraorbital hemangioma with exophthalmia, improvement with propranolol was dramatic, with exophthalmia disappearing after 2 weeks of treatment.

In 4 patients with subglottic hemangiomas, the efficacy of propranolol treatment was spectacular (Figure 1). Three patients without previous treatment who were admitted for respiratory distress and feeding intolerance were administered propranolol and a short course of corticosteroids (<1 week) that allowed stridor resolution, the possibility to feed orally, and discharge home. These 3 children underwent no endoscopic hemangioma debulking, intralesional corticosteroid injections or long-term corticotherapy, or vincristine administration. They were treated with propranolol and oral prednisone during the acute phase to control dyspnea and were weaned off oral corticotherapy before discharge home. This therapy lasted less than 1 week, and no recurrence resulted from discontinuation of corticosteroids. The first-week response can be attributed to the effect of corticosteroids and propranolol, but the sustainability of results is due to the effect of propranolol. In the case of mild dyspnea associated with early discovery of a subglottic hemangioma, we believe that propranolol can be tried alone. Because these children were in respiratory distress and we wanted to avoid intubation, they received corticosteroids for a few days. The remaining child had a circumferential subglottic hemangioma that had been endoscopically debulked and injected with corticosteroids. The patient’s stridor recurred and disappeared with propranolol treatment. A fifth child with subglottic hemangioma was 14 months old and had undergone multiple laser treatments and a tracheotomy. Endoscopy showed tracheomalacia and subglottic stenosis associated with a residual hemangioma. Numerous medical and surgical therapeutic options (endoscopic approaches and external surgical excisions)\textsuperscript{14-16} are available to treat subglottic hemangiomas. However, these treatments and their potential risks and adverse effects may be avoided with the use of propranolol, which may be considered first-line treatment in patients with airway hemangiomas, followed by a short course of systemic corticosteroids to control initial stridor.\textsuperscript{17}

Fifteen children herein had undergone previous treatments, mainly intralesional or general corticosteroids; however, these treatments had been stopped, and they were treated only with propranolol during the study. Three children (patients 2-4) had a short course of general corticosteroids to control initial stridor. The advantage of propranolol over general corticosteroids is its good tolerance, allowing prolonged treatment. Among patients in whom there is a good response to oral corticosteroids, treatment often has to be stopped, with frequent relapse. Because propranolol is well tolerated, it can be given for a long period, avoiding relapse.

Apart from efficacy, good tolerance is essential to evaluate a treatment. Propranolol has been used for more than 40 years in infants with cardiac problems and has a well-documented safety and adverse event profile. Potential adverse effects of β-blockers include bradycardia, hypotension, hypoglycemia, gastrointestinal discomfort, and bronchospasm. In our series, propranolol treatment never had to be stopped because of complications, and the only adverse effects noted were sleeping disturbances (insomnia) in 7 children and mild diarrhea in 2 children. These are not the usual adverse effects reported in the literature for propranolol.\textsuperscript{18,19} For this indication, the most frequently reported adverse effects are hypotension and bradycardia, described as lethargy, coldness, and hypoglycemia, which is why treatment is initiated using a protocol in which gradual dosage increases are achieved once contraindications have been excluded (see the “Treatment Protocol” subsection of the “Methods” section). Moreover, parental guidance about the clinical signs of bradycardia, hypotension, and hypoglycemia should be provided. No clinical signs of hypoglycemia were noted in our series when children were fed normally, but parents were advised to stop treatment in the case of fasting. The risk-benefit profile of propranolol was excellent, with no adverse effects or mild side effects that did not interrupt therapy. Treatment monitoring varies among institutions. With our protocol, we would have detected only clinically apparent signs of bradycardia, hypotension, and hypoglycemia, and these signs may be masked due to the β-blocking effect of propranolol. Future studies should determine whether the established safety of propranolol is valid for this off-label indication.

The safety and good tolerance of propranolol treatment led us to extend the indication of treatment to
mangiommas; indeed, the severity of adverse effects of β-blockers seemed disproportionate with those of high-dose prolonged corticosteroid therapy. Twenty-six hemangiommas were treated with propranolol at locations for which long-term corticosteroid treatment previously would not have been initiated (nose, lips, and parotid area) unless a complication had occurred (ulceration or bleeding). This treatment allowed rapid control and regression of the lesion, with less functional and esthetic impairment (Figure 2). This indication and expansion of the use of propranolol for head and neck hemangiommas may be considered, but it is important to proceed with caution because β-blockers potentially can have severe adverse effects, and our experience using this medication in patients without cardiac problems and without cardiac monitoring is limited.

The mechanisms of β-blocker action on infantile hemangiommas are unknown. Theories have been proposed, including cellular apoptosis, the effect of vasoconstriction and hypoxia, and downregulation of basic fibroblast growth factor and vascular endothelial growth factor. In conclusion, propranolol seems to be an effective treatment of head and neck infantile hemangiommas, especially when started early within the rapid growth phase. Relapse was avoided if treatment was prolonged after involution of the lesion (age 12 months). Propranolol is our first-line therapeutic choice for head and neck hemangiommas. It is a promising treatment of subglottic hemangiommas or lesions involving the orbit. Moreover, the effectiveness of propranolol has led to treatment of hemangiommas in locations that previously did not benefit from medical therapy because of possible adverse effects. Multicenter prospective studies should elucidate optimal dosing and age at treatment cessation.

Submitted for Publication: April 3, 2010; final revision received January 18, 2011; accepted February 9, 2011.

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Critical revision of the manuscript for important intellectual content: Fuchsmann, Ayari-Khalfallah, Powell, and McConne. Administrative, technical, and material support: Giguerre. Study supervision: Froehlich.

Financial Disclosure: None reported.

Previous Presentation: This study was presented at the American Society of Pediatric Otolaryngology annual meeting; May 1, 2010; Las Vegas, Nevada.

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