Propranolol in the Management of Airway Infantile Hemangiomas

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Objective: To report our experience with propranolol in managing airway infantile hemangiomas.

Design: Case series of 3 consecutive patients who had extensive, symptomatic airway infantile hemangiomas treated with propranolol.

Setting: Tertiary academic medical center.

Patients: Three infants with facial cutaneous hemangiomas who developed stridor that progressed to respiratory distress, which according to laryngoscopic examination results was confirmed to be caused by extensive subglottic hemangiomas. These patients underwent follow-up during their course of therapy, ranging from 3 weeks to 15 months.

Results: Patient 1 failed to respond to systemic corticosteroids, laser ablation, and intravenous vincristine for her airway hemangioma and had to undergo tracheotomy. She was given propranolol after her tracheotomy and had a significant reduction in her subglottic airway obstruction. Patient 2 developed progressive stridor secondary to airway hemangioma at age 6½ months following tapering of systemic corticosteroids prescribed for her periorbital hemangioma. Systemic corticosteroids were restarted with the addition of propranolol. The stridor improved within 24 hours, and she was able to be weaned off corticosteroids. Patient 3 was also treated with initial combined therapy of systemic corticosteroids and propranolol. He had a significant reduction in stridor within 24 hours and was weaned off corticosteroids.

Conclusions: Our 3 patients had severe respiratory symptoms related to their airway infantile hemangiomas. In the first patient, propranolol was used when other treatments were ineffective or associated with intolerable adverse effects. In the second and third patients, propranolol was part of a dual regimen that resulted in rapid resolution of airway symptoms and allowed for quicker weaning of corticosteroids.


MANAGEMENT OF AIRWAY INFANTILE HEMANGIOMA (IH) CAN BE CHALLENGING. MULTIPLE MODALITIES, BOTH MEDICAL AND SURGICAL, HAVE BEEN USED; MANY HAVE SIGNIFICANT RISKS AND COMPLICATIONS. UNTIL RECENTLY, THE MOST COMMON MEDICAL THERAPY USED WAS HIGH-DOSE SYSTEMIC CORTICOSTEROIDS, BUT THIS OFTEN RESULTS IN SIGNIFICANT WELL-KNOWN ADVERSE EFFECTS INCLUDING HYPERTENSION, IRRITABILITY, AND CUSHINGOID APPEARANCE. EXPERIENCE HAS BEEN GROWING WITH AN ALTERNATIVE MEDICAL TREATMENT, PROPRANOLOL, FOR MANAGEMENT OF IH. THERE HAVE BEEN REPORTS OF DRAMATIC RESPONSE TO BOTH CUTANEOUS AND AIRWAY IH WITHIN DAYS OF STARTING PROPRANOLOL THERAPY. PROPRANOLOL IS AN ATTRACTIVE THERAPEUTIC ALTERNATIVE BECAUSE IT CAN AVOID THE COMMON ADVERSE EFFECTS OF PROLONGED HIGH-DOSE STEROID USE, BUT IT IS NOT WITHOUT ITS OWN POTENTIAL RISKS INCLUDING BRADYCARDIA, HYPTENSION, AND HYPOGLYCEMIA AS WELL AS POTENTIAL EXACERBATION OF REACTIVE AIRWAYS DISEASE. CHILDREN RECEIVING THIS THERAPY MUST BE MONITORED CLOSELY, AND ADVERSE EFFECTS ALREADY HAVE BEEN REPORTED.

We now report the clinical course in 3 cases of airway IH managed with propranolol. This study was approved by the University of California, San Francisco, Committee on Human Research.

REPORT OF CASES

CASE 1

Patient 1 was born with a faint vascular birthmark involving the right temple with slight extension into the preauricular skin. She was admitted to our institution at age 5 weeks owing to acute respiratory distress including stridor and desaturations. Evaluation of her airway at that time using laryngoscopy revealed a bilat-
eral subglottic IH (Figure 2). Sizing of the airway was not performed during the laryngoscopic examination to minimize further airway edema and respiratory distress. Treatment with oral prednisolone was started at 3 mg/kg/d, which initially resulted in improvement of her airway symptoms. However, she continued to have intermittent stridor and desaturations, and according to a laryngoscopic examination repeated 9 days later, there was minimal response to her high-dose corticosteroids (Figure 3). Therefore, unilateral carbon dioxide laser ablation was performed at age 2 months (Figure 4). A 3.5-mm cuffed endotracheal tube with an outer diameter of 4.9 mm was passed through the subglottis after the procedure. She was discharged within a few days and was prescribed the same steroid regimen she had been given previously.

Figure 1. Cutaneous hemangiomas in patient 1 at age 5 weeks.

Figure 2. Subglottic airway at initial laryngoscopic examination before any treatment in patient 1 at age 5 weeks.

Figure 3. Subglottic airway in patient 1 after 1 week of high-dose prednisolone treatment (A) and closer view of subglottic airway (B).
The infant was readmitted 6 weeks later after the development of an upper respiratory tract infection and increasing stridor and retractions. She had also developed hypertension and severe cushingoid features. A subsequent laryngoscopic examination demonstrated persistent subglottic obstruction and significant upper airway obstruction on induction. The latter was thought to be worsened by extrinsic soft-tissue mass effect, resulting in oropharyngeal, pharyngeal, and hypopharyngeal collapse. A nasal trumpet was placed in the operating room, which greatly improved her obstruction and desaturations and was used for approximately 6 weeks while she was an outpatient. A discussion was held with the family about the findings and the recommendation to taper off corticosteroids owing to the adverse effects. Both tracheotomy and vincristine were offered as possible treatment options. This discussion was carried out in March 2008, before widespread knowledge of the encouraging results of the use of propranolol for treatment of IH. The family ultimately chose to proceed with vincristine; 6 weekly doses of vincristine at 0.05mg/kg were given. The infant was still undergoing a steroid taper during this time. She underwent another laryngoscopic examination at age 5 months and symptomatically did not appear improved after vincristine treatment. She appeared to have a 2-mm airway, and the presumption was that she was having rebound growth due to the steroid taper. She therefore underwent a tracheotomy (Figure 5). At age 6 months, she was given propranolol at 1.8 mg/kg 3 times per day for treatment of the airway IH and to help control the steroid-induced hypertension. This coincided with the early verbal reports of success with propranolol therapy for IH. The propranolol was continued twice a day owing to slightly low blood pressure. During her hospitalization, she was evaluated by a cardiologist and underwent an echocardiogram as part of her evaluation for PHACE syndrome (posterior fossa malformation, hemangioma, arterial anomalies, cardiac anomalies, eye anomalies) but did not have any other specific monitoring while receiving propranolol. The propranolol was continued until age 13 months, at which time she no longer had any signs of her prior cushingoid appearance. At age 15 months, the patient’s airway IH had sufficiently involuted, as observed on a subsequent laryngoscopic examination, and her airway had stabilized (Figure 6). The tracheotomy was removed at that time. The propranolol was tapered for 3 more weeks and then discontinued. The patient is currently doing well without airway symptoms.

In addition to these morbidities, evaluation for PHACE syndrome revealed mild structural anomalies in the cerebrovascular arterial system (slight attenuation of the distal cervical right internal carotid artery) but no other abnormalities. Magnetic resonance imaging revealed an additional hemangioma in the left orbit.
CASE 2

Patient 2 had a faint telangiectatic vascular stain at birth involving the right temple with focal extension into the right preauricular area, right postauricular scalp, and posterior aspect of the neck (Figure 7). The patient had had an uneventful perinatal history. At age 7 weeks, she had swelling of the right upper eyelid and was given the diagnosis of IH by the pediatric dermatologists. To limit ocular risk, oral prednisolone at 2 mg/kg/d was prescribed. From ages 7 weeks to 8 months, the patient did not undergo follow-up at our institution. At age 8 months, she was admitted to a pediatric intensive care unit at an outside institution for worsening stridor and sternal retractions. A history revealed that she had been having intermittent stridor with agitation for the prior 1 1/2 months since corticosteroids had been stopped. She was treated with methylprednisolone, racemic epinephrine, and ranitidine. Evaluation by an otolaryngologist via a flexible laryngoscope revealed 60% to 80% subglottic obstruction with a submucosal mass consistent with subglottic hemangioma. Tracheotomy was recommended, but the parents requested a second opinion and transfer to our institution. During the patient's admission to our institution, telangiectasias and fullness of the right preauricular region extending inferiorly along the neck were noted, as well as intermittent faint inspiratory stridor. Intravenous dexamethasone was administered. Two days following her admission, a laryngoscopic examination was performed and revealed 80% to 90% subglottic obstruction with a mass consistent with IH (Figure 8). The patient failed to respond to extubation in the operating room and underwent intubation at the conclusion of the procedure. She self-extubated that evening and was observed to have mild inspiratory stridor with agitation. The following day, propranolol at 1 mg/kg 3 times per day was started along with prednisolone at 3 mg/kg twice a day. The decision was made to start dual therapy to maximize therapeutic potential to improve the patient’s air-

Figure 7. Cutaneous hemangiomas in patient 2 at age 8 months.

Figure 8. Subglottic airway in patient 2 before treatment at age 8 months (A) and closer view of subglottic airway (B).
Airway IH can be life-threatening. Multiple medical treatments have been tried, including high-dose corticosteroids, intralesional corticosteroids, interferon alfa, and vincristine, but all have significant potential toxic effects.1,11-14 Systemic corticosteroids can be effective in halting further growth of IH during the proliferative phase, with success rates ranging from 60% to 90%.13,15 However, efficacy rates may be lower in large, function-threatening IH, and adverse effects may be intolerable.15,16 Interferon was widely heralded for treatment in refractory IH12,17-22 but has a significant risk of neurotoxic effects, especially in very young infants.12 Vincristine is another chemotherapeutic agent that has been reported to be effective, but experience with vincristine in the treatment of IH is not extensive. Adverse effects include peripheral neuropathy and electrolyte imbalances, and yet another downside of vincristine is that it requires administration via central line placement.13,21,22

Many surgical approaches also have been attempted, especially in cases that are unresponsive or partially responsive to medical therapies. These include laser ablation (carbon dioxide, Nd:YAG, and potassium-titanyl-phosphate lasers) and tracheotomy.13 Laser ablation is considered a reasonable option for a more localized airway IH that is not causing extreme airway narrowing. A patient with an extensive, circumferential IH with critical airway narrowing would not be a good candidate for laser debulking owing to the risk of scarring resulting in subglottic stenosis.13 Submucosal resection through a laryngofissure also has been tried, but there are limited outcomes studies analyzing the success of this method.23

Because IH is known to undergo initial rapid proliferation followed by a slower involution, the primary goals of treatment of airway IH are to provide an adequate airway during the proliferative period, avoid life-threatening obstruction, and minimize therapies that may result in long-term complications. Tracheotomy is no longer considered to be a first-line treatment because of the associated morbidity, labor required to care for the patient after tracheotomy, and risk of mortality (currently approximately 25% to 30%) (Figure 11B). At age 2 months, he was weaned off the oral corticosteroids while continuing to receive propranolol at 2 mg/kg/d. He remained asymptomatic until age 4½ months, when he developed symptoms of an upper respiratory tract infection and had progressive worsening of stridor and cough. He also developed an ulcer on the soft palate. He was admitted and given prednisolone at 3 mg/kg/d, and his symptoms resolved within 24 hours. At 10 days of follow-up, the ulcer had healed and he continued to have no stridor. He is currently being weaned off of the corticosteroids.

As part of the PHACE workup, an ophthalmologic evaluation was performed and revealed morning glory disc anomaly, a finding reported in the context of PHACE syndrome.9,10 Results of an echocardiogram were unremarkable. Magnetic resonance imaging and magnetic resonance angiography will be performed in the future to rule out other possible PHACE associations.

**CASE 3**

Patient 3 was born with telangiectasias and vasoconstriction in a segmental distribution on the upper chest, ears, and mandibular areas. These vascular stains were consistent with IH precursor lesions that proliferated during the following 2 weeks and ultimately involved the bilateral mandibular area (or so-called beard distribution), lower lip, tongue, gingiva, and anterior part of the chest (Figure 10). At age 3 weeks, he went to an outside institution with a 2-day history of biphasic stridor and retractions, prompting admission to the neonatal intensive care unit. A laryngoscopic examination was performed the day after admission, and 80% obstruction of the subglottis with a mass consistent with IH was observed (Figure 11A). He had worsening stridor with retractions immediately after the procedure and required continuous positive airway pressure for airway support overnight. He was given prednisolone at 3 mg/kg twice a day and propranolol at 2 mg/kg 3 times per day. Within 24 hours, the stridor and retractions resolved. A laryngoscopic examination performed 1 week later demonstrated significant improvement in the subglottic airway, with subglottic narrowing reduced to approximately 20% (Figure 11B). He was discharged the following day and has remained asymptomatic. Her corticosteroids were weaned at age 13 months, and she is now age 18 months old and approximately halfway through her propranolol wean without recurrence of stridor or respiratory distress.

Because of the segmental facial distribution of this patient’s IH, an evaluation for PHACE syndrome was undertaken and revealed no structural anomalies. However, magnetic resonance imaging did show evidence of IH in the right supraorbital area and multiple IHs in various parts of the right side of the face and neck, with the biggest single nodule measuring 3 cm in the right parotid gland.

**COMMENT**

Airway IH can be life-threatening. Multiple medical treatments have been tried, including high-dose corticosteroids, intralesional corticosteroids, interferon alfa, and vincristine, but all have significant potential toxic effects.1,11-14 Systemic corticosteroids can be effective in halting further growth of IH during the proliferative phase, with success rates ranging from 60% to 90%.13,15 However, efficacy rates may be lower in large, function-threatening IH, and adverse effects may be intolerable.15,16 Interferon was widely heralded for treatment in refractory IH12,17-22 but has a significant risk of neurotoxic effects, especially in very young infants.12 Vincristine is another chemotherapeutic agent that has been reported to be effective, but experience with vincristine in the treatment of IH is not extensive. Adverse effects include peripheral neuropathy and electrolyte imbalances, and yet another downside of vincristine is that it requires administration via central line placement.13,21,22

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estimated risk to be approximately 1%).\textsuperscript{1,15} Until recently, systemic corticosteroids, intralesional corticosteroids, and/or laser ablation have generally been used first to control airway disease.\textsuperscript{24,25} The addition of propranolol as another therapeutic option has been met with great enthusiasm, and the limited evidence to date suggests that it is a promising agent\textsuperscript{4-7,26-29} (Table).

Sans et al\textsuperscript{,7} in their most recent review of 32 children with IH involving a variety of anatomical sites treated with propranolol at 2 to 3 mg/kg/d, report functional improvement occurring within hours of starting the medication and long-term efficacy reaching 100%. The average age at the start of treatment was 4 months, with at least half of the patients able to discontinue treatment within 6 months. Patients receiving high-dose systemic corticosteroids were able to be weaned off of them within a few weeks. The monitoring policy used in that study, which was more stringent than the one we currently use at our institution, included an initial electrocardiogram and echocardiogram for all patients before starting therapy, then inpatient blood pressure and heart rate monitoring for the first 6 hours, followed by outpatient monitoring after 10 days and then monthly. Perhaps one of the most remarkable findings of the study by Sans et al was that propranolol appeared to shorten the natural course of IH involution. This distinguishes it from other medical therapies for IH, which were found to be effective only during the proliferative growth phase.\textsuperscript{25} The causes for this dramatic response of IH to propranolol are continuing to be investigated. Proangiogenic factors are known to be involved in the regulation of IH growth. Investigators have also found \( \beta\)-adrenergic receptors on endothelial cells of IH and shown that \( \beta\)-blockade may lead to apoptosis of capillary endothelial cells.\textsuperscript{7}

Several articles in the literature now report the use of propranolol in the management of airway IH, including one in which propranolol was used as the initial and sole therapy.\textsuperscript{5,7,27,28} In the study by Buckmiller et al,\textsuperscript{28} although the authors recommend that propranolol be used as a first-line treatment in symptomatic airway IH, it was used only after failure of high-dose corticosteroids and vincristine, as in the case of our first patient. In our experience, it is still too early to recommend the sole use of propranolol in the management of symptomatic airway IH. In our first patient, systemic corticosteroids had to be discontinued because she developed hypertension.
and such striking cushingoid features that the external soft tissues exacerbated her airway obstruction. Adjuvant therapies with partial carbon dioxide laser ablation and vincristine infusions were not successful; therefore, she underwent tracheotomy. She was started on propranolol to control her hypertension. This was also around the same time as early verbal reports of propranolol’s effectiveness in treating IH, and thus potentially reducing the period of time necessary for tracheotomy. It is unclear whether the propranolol had any significant effect on the involution of her airway IH, allowing for earlier decannulation, or whether she would have undergone decannulation at the same time without propranolol therapy given the natural history of hemangioma to involute with time. However, other investigators have demonstrated the effectiveness of propranolol therapy in both the proliferative and involutorial phases of IH.7

Our second and third patients had severe respiratory distress and critical airway narrowing from IH and were given dual therapy with high-dose corticosteroids and propranolol. In this way, we were able to maximize the rapid therapeutic effects of propranolol while remaining cautious owing to our limited prior experience with this drug (especially because of the potentially serious adverse effects of propranolol in the infant younger than 3 months, including bradycardia, hypotension, and hypoglycemia). Both these patients demonstrated a dramatic improvement in airway symptoms within 24 hours and then were able to be weaned off their high-dose corticosteroids, thereby avoiding potentially dangerous adverse effects while they were receiving propranolol. Propranolol appears to be a promising therapeutic option for IH. We remain reluctant to propose propranolol as a sole first-line treatment for symptomatic airway IH, however. Although early results are encouraging, experience remains limited. Potential risks include bradycardia, hypotension, and hypoglycemia, particularly in infants younger than 6 months. Moreover, currently no uniform consensus exists regarding dosing and monitoring protocols, with recommendations varying from obligatory pretreatment admission and pediatric cardiologist consultation to outpatient parental monitoring.7,26,30

To date, our approach at the University of California, San Francisco, has been to recommend particularly close monitoring with inpatient observation for patients with symptomatic airway disease or infants younger than 3 months who are treated with propranolol. Those who do not have severe airway symptoms and are older than 3 months are given slowly increasing dosages of propranolol beginning with 0.3 mg/kg/d divided every 8 hours, with increases every 3 days in increments of 0.3 mg/kg to a target dosage of 2 mg/kg/d. For infants, more rapid increases in dosing can be used with initial dosing at 1 mg/kg/d, increasing to 2 mg/kg/d a few days later. We also recommend that infants younger than 6 months be fed every 3 to 4 hours to avoid drug-induced hypoglycemia. Heart rates are monitored either at home or by primary care physicians every few days to ensure that bradycardia does not develop. Using this regimen, we have treated 18 patients with both cutaneous and airway IH at our institution. Of these, 1 child developed otherwise unexplained bradycardia and hypoglycemia requiring brief hospitalization. Recovery was rapid, and no other serious toxic effects have been noted. A dose reduction was required for one patient with a mild decrease in blood pressure and in another for excessive sleepiness without an objective change in vital signs. A few parents have reported sleep disturbances, a known but infrequently reported adverse effect of the medication.

<table>
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<th>Source</th>
<th>No. of Patients</th>
<th>Average Age at Start of Propranolol Treatment, mo</th>
<th>Location of IH</th>
<th>Dosage, mg/kg/d</th>
<th>Average Length of Treatment</th>
<th>Outcomes</th>
<th>Adjuvant Treatment</th>
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<td>Multiple sites</td>
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<td>13 of 32 study patients underwent adjuvant systemic corticosteroid treatment</td>
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<td>Beard, larynx</td>
<td>2</td>
<td>6 mo</td>
<td>Healed ulceration, resolution of dyspnea</td>
<td>Partial involution</td>
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Abbreviation: IH, infantile hemangioma.

aAcetobutolol.
In conclusion, we report 3 cases of airway IH and our experience with the use of propranolol as part of their management. This medication is an exciting potential therapy for airway IH. However, controlled trials and long-term follow-up are warranted to assess efficacy and potential toxic effects in comparison with other modalities of treatment and to determine whether propranolol can be considered a safe and an effective alternative for first-line treatment for airway IH.

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Author Contributions: Drs Rosbe, Suh, and Meyer had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rosbe, Suh, and Meyer. Acquisition of data: Rosbe, Meyer, Maguiness, and Frieden. Analysis and interpretation of data: Rosbe, Meyer, and Frieden. Drafting of the manuscript: Rosbe, Suh, Meyer, and Maguiness. Critical revision of the manuscript for important intellectual content: Rosbe, Suh, Meyer, and Frieden. Administrative, technical, and material support: Suh and Maguiness. Study supervision: Rosbe, Meyer, and Frieden.

Financial Disclosure: Dr Frieden has served as a consultant to Pierre-Fabre Dermatology, which holds a patent for the treatment of hemangiomas with propranolol and is launching clinical trials to study this medication as a hemangioma treatment.

REFERENCES