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Propranolol for the treatment of airway hemangiomas: A case series and treatment algorithm

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ABSTRACT

Objectives: (1) To present six patients with symptomatic airway hemangiomas treated with oral propranolol. (2) To review the diagnostic and treatment options for airway hemangiomas and propose a new management protocol.
Study design: Retrospective review.
Setting: Tertiary care children's hospital.
Subjects and methods: Pediatric patients diagnosed with obstructive airway hemangiomas treated with oral propranolol. Patients were followed for symptomatic improvement and relief of airway obstruction on imaging or laryngoscopy.
Results: Seven patients presenting with airway obstruction were treated with propranolol. One patient had a focal hemangioma confined to the subglottis. Four patients had airway hemangiomas that extended beyond the confines of the larynx and trachea. A sixth patient had a bulky supraglottic hemangioma. A seventh patient with an extensive maxillofacial lesion failed propranolol therapy and was found to have a pyogenic granuloma on final pathology after excision. Six patients had failed standard medical therapy and/or surgical interventions and were treated successfully with oral propranolol with improvements in airway symptoms and oral intake, requiring no further surgical intervention. Treatment was initiated as early as 1.5 months of age, and as late as 22 months. No adverse side effects of propranolol were noted.
Conclusions: Oral propranolol was successfully used to treat airway hemangiomas, resulting in rapid airway stabilization, obviating the need for operative intervention, and reducing the duration of systemic corticosteroid therapy while causing no obvious adverse effects. These outstanding results enable the possibility of use of a standardized diagnostic and treatment algorithm for airway hemangiomas that incorporates systemic propranolol.

1. Introduction

Infantile hemangiomas (IH), also known as juvenile hemangiomas, are the most common tumor of infancy, with a natural course of three phases; proliferation, involution, and involuted. Histologically, IH are characterized during proliferation by high mitotic rates of endothelial cells within capillaries, followed by apoptosis and replacement with fibrofatty tissue as involution progresses [1]. Immunohistochemistry further characterizes these tumors for the presence of endothelial cells with immunoreactivity to the erythrocyte-type glucose transporter protein isoform 1, or GLUT-1 [2]. When involving the airway, growth can be very threatening, leading to obstructive airway compromise, stridor, and oral intolerance. Though subglottic hemangiomas (SH) are more emphasized in the literature, hemangiomas may occur throughout the airway resulting in similar symptoms of airway distress and feeding difficulties. Treatment options include medical therapies, with systemic and intralesional corticosteroids being the mainstay, while interferon α and vincristine are other options.

Surgically, treatment options include obtaining a definitive airway with a tracheotomy until involution, or partially destructive

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Table 1
Patient data.

Patient	Age at Dx (months)	Gender	Diagnostic studies	Location of infantile hemangioma	Other treatments received	Age at initiation of propranolol (months)	Duration of therapy (months)	Symptomatic improvement from propranolol	Follow up (months)
1	1	F	NP/CT/MR/DL	Skin, parotid, deep neck, pharynx, glottis, subglottis, trachea	1. Systemic steroids 2. Intralesional steroids 3. Tracheotomy	18	10	Airway obstruction relieved. Trach capped after 3 weeks. Decannulated after 4 months. Regression of cutaneous lesions.	14
2	2	F	NP/CT/DL	Supraglottis, subglottis, glottis, deep neck, parotid gland, skin	1. Systemic steroids 2. Intralesional steroids	6	6	Airway obstruction relieved. Symptomatic improvement after 1 week. Regression of parotid and cutaneous lesions.	13
3	1	F	NP/CT/DL	Subglottis, glottis	1. Systemic steroids 2. Intralesional steroids	2	6	Airway obstruction relieved. Symptomatic improvement after 1 week.	10
4	3	F	NP/MR/DL	Subglottis	1. Systemic steroids 2. CO_2 laser excision	5	6	Airway obstruction relieved. Symptomatic improvement after 1 week.	8
5	3	F	NP/MR/DL	Supraglottis: left aryepiglottic fold	1. Systemic steroids	22	6	Airway obstruction relieved. >30% reduction in size of lesion. Symptomatic improvement after 2 weeks.	6
6	1	F	NP/MR/DL	Subglottis, deep neck, mediastinum	1. Systemic steroids 2. Intralesional steroids 3. Open subglottic resection	4	5	Airway obstruction relieved. >50% reduction in size of lesion within 1 week. Symptomatic improvement after 1 week.	10
7	0.5	F	NP/MR/CT	Maxillofacial: left nasal cavity, maxilla	1. Systemic steroids	1.6	N/A	N/A	Did not complete therapy[a]

Dx: diagnosis; NP: nasopharyngoscopy; CT: computer tomography; MR: magnetic resonance; DL: direct laryngoscopy; N/A: not available.
[a] See discussion for patient details.

or excisional procedures [3]. Laser excision is commonly performed, though often surgical management does not obviate the need for systemic corticosteroids throughout a patient's treatment course [4]. In the subglottis, serial procedures in the airway increase the risk of scarring and subsequent subglottic stenosis [5].

Propranolol has become an emerging treatment option for hemangiomas since Leaute-Labreze's report of eleven patients with infantile hemangiomas successfully treated with propranolol [6]. Denoyelle et al. report two patients with subglottic hemangiomas successfully treated with propranolol [7]. Buckmuller et al. reported one patient with a subglottic hemangioma with similar success [8]. We have previously described a case of a life threatening hemangioma of the airway successfully treated with propranolol [9]. In this report, we present seven patients with symptoms of airway obstruction, clinically diagnosed with IH of the upper and lower airway, treated with propranolol. As propranolol becomes a mainstay of treatment, we discuss the role that surgical therapies and corticosteroids play in the treatment of hemangiomas of the airway, and propose a diagnostic and therapeutic algorithm.

2. Materials and methods

A retrospective chart review of patients presenting with airway obstruction, clinically diagnosed with infantile hemangioma of the airway that were treated with propranolol from October 2008 to June 2009 was performed. Children were identified from the department of pediatric otolaryngology at Lucille Packard Children's Hospital and Seattle Children's Hospital. Chart review of clinic, in-patient, operative reports, radiological and pathology reports were performed. Institutional review board approval was obtained from the Stanford University Research Compliance Office, Human Subjects Research Office and the Subjects Protection Program (HSPP), Seattle Children's Hospital. Parents were given informed consent of the off label use of propranolol.

3. Results

Patient demographics and data are presented in Table 1. Seven patients were clinically identified with an airway hemangioma. One patient with a maxillofacial lesion presented with oral and nasal airway obstruction, and diagnostic imaging was consistent with a hemangioma. The patient did not respond to propranolol therapy, underwent excision, and on final pathology was found to have a pyogenic granuloma; GLUT-1 staining was negative and these results were further confirmed at the Mayo Clinic. All patients were female with an average age of presentation of 1.6 months (1–3 months). Two patients were identified as premature at birth. All patients presented with airway obstruction. Six patients had clinically significant relief of symptoms of airway obstruction after treatment with propranolol, with follow up ranging from 6 to 14 months. Clinical responses were noted within 1–3 weeks from initiation of propranolol. Relief of obstruction led to decrease in stridor, decannulation, and avoidance of further airway procedures.

Diagnostic evaluation involved nasopharyngoscopy (NP) in all patients, and all patients underwent some type of imaging exam, completing computer tomography [10] ($n = 3$) and/or magnetic resonance (MR) imaging ($n = 4$). Two patients who required sedation for their imaging studies were intubated to stablize the airway during the study. Five patients had airway obstruction at the level of the subglottis, though three of the five patients had IH that extended beyond the subglottis (Figs. 1, 2 and 4). One patient was found to have a supraglottic IH along the left aryepiglottic fold resulting in progressive symptoms of obstructive sleep apnea (Fig. 3). The seventh patient presented with nasal and oral airway

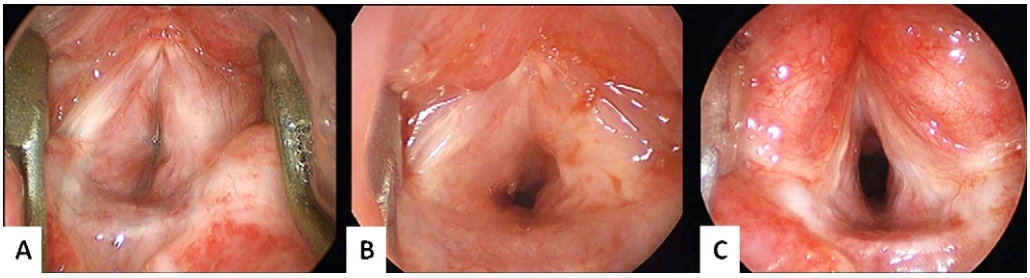

Fig. 1. Patient 1 direct laryngoscopy. Prior to propranolol therapy, bilateral subglottic hemangioma with near complete airway obstruction. The patient has a tracheotomy in place (A). After 2 weeks of propranolol, demonstrating an airway lumen, tracheotomy is in place (B). Patient was decannulated after 4 months of propranolol therapy. After 10 months of propranolol, patient had significant improvement in airway lumen (C).

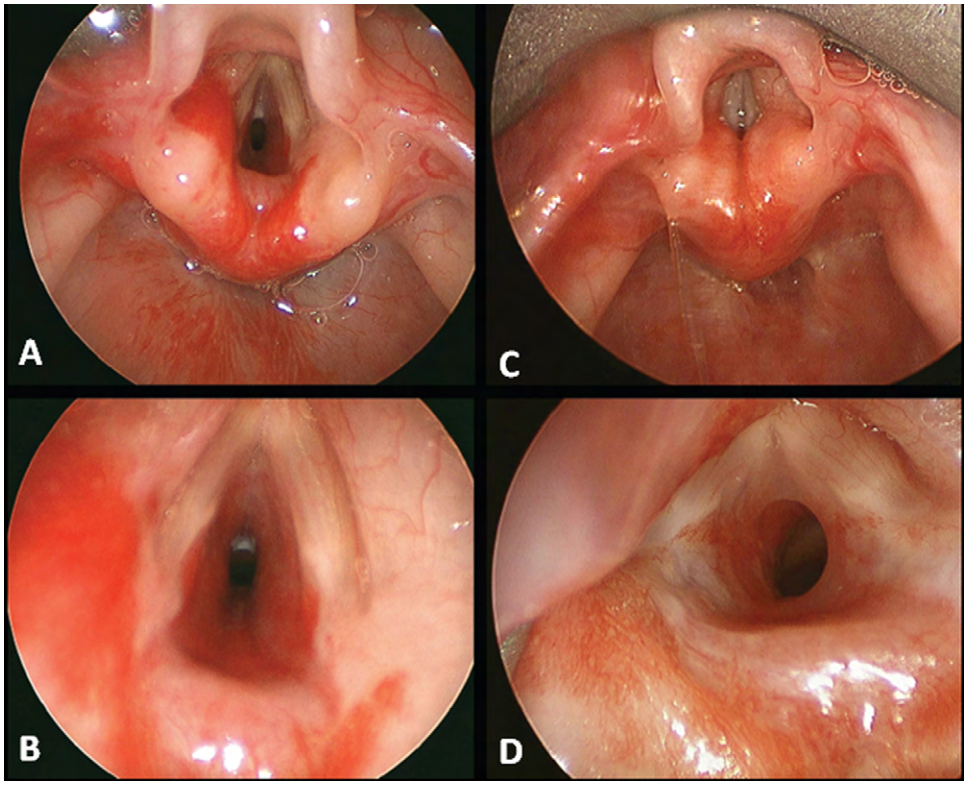

Fig. 2. Patient 2 direct laryngoscopy. Prior to propranolol therapy, hemangioma noted in the subglottis and on supraglottic mucosa bilaterally (A), magnified view (B). After 2 weeks of propranolol therapy, there is significant improvement in subglottic airway and less supraglottic mucosal involvement (C), magnified view (D).

obstruction from an extensive maxillofacial lesion with compressive symptoms. This seventh patient did not respond to propranolol therapy, underwent wide excision of the lesion which on pathology was found to be a pyogenic granuloma, negative for GLUT-1.

All patients were treated with systemic or intralesional corticosteroid treatment (prednisolone 3 mg/kg/day given daily or bid and/or injected Kenalog 40 mg/ml), for variable durations ranging from 1 to 7 months prior to or concurrent with oral propranolol therapy. Side effects attributed to long-term systemic corticosteroid therapy included Cushingoid facies ($n = 4$), immune deficiency ($n = 1$), and muscle weakness ($n = 1$). Four patients had undergone intralesional steroid injection prior to propranolol therapy. Three patients had surgical procedures for their airway hemangioma (AH), not including biopsy; one patient underwent CO_2 laser excision of a subglottic lesion, one patient had an open resection of a subglottic lesion with laryngotracheoplasty, and a third patient required a tracheotomy to secure the airway before propranolol was initiated. Four patients underwent biopsy with confirmation of the pathological diagnosis of IH by histology and the presence of GLUT-1 immunohistochemical staining.

Prior to the initiation of oral propranolol, all patients completed a cardiologic evaluation. All patients completed EKGs, and six patients had baseline blood pressure measured, though blood pressure was unobtainable for one patient despite several attempts. Four patients had a complete evaluation by a cardiologist prior to initiation of propranolol. One patient was started on therapy in an in-patient hospital stay, while six were started in an outpatient setting. No hypotension from propranolol therapy occurred and no adverse side effects were reported. Parents were advised to give the patients oral propranolol with meals, and none of the patients developed symptomatic hypoglycemia. Propranolol was given in liquid form, 2 mg/kg/day divided three times a day for 5–10 months of therapy. Patient 1 had significant improvement in

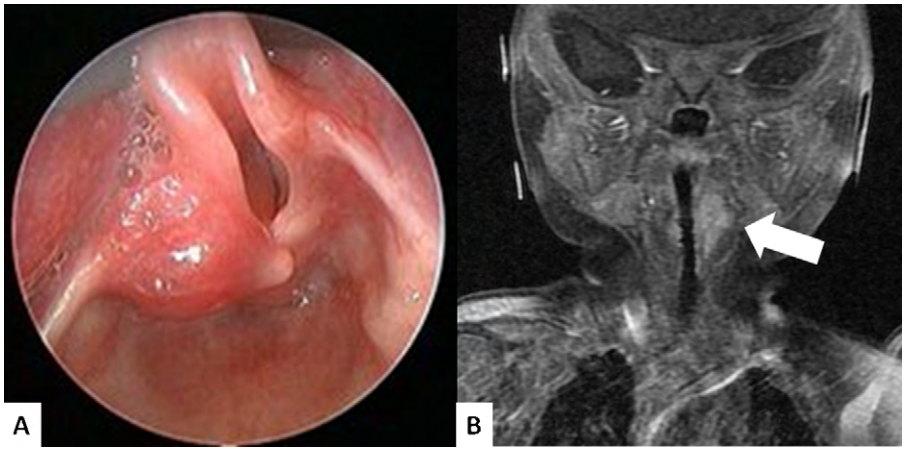

Fig. 3. Patient 5 direct laryngoscopy. Supraglottic hemangioma located along the right aryepiglottic fold and anterior surface of the epiglottis compressing on the supraglottic airway (A). On coronal imaging MRI, the lesion is seen extending into paraglottic space (arrow) and possibly to the contralateral paraglottic space (B). Post propranolol imaging not available.

airway obstructive symptoms after 6 months of therapy, though propranolol was continued for 10 months total. The age at initiation of oral propranolol ranged from 1.5 to 22 months of age.

4. Discussion

In this series, six patients with hemangiomas of the airway were treated with propranolol resulting in significant relief of airway obstruction. Propranolol therapy allowed for decannulation, avoided further surgical interventions, and allowed for the tapering of systemic corticosteroid therapy. One patient initiated treatment at 22 months of age when symptoms of obstructive sleep apnea became more severe. Though the patient had an improvement in symptoms and a reduction in size of IH after the initiation of propranolol, it is impossible to differentiate the response from any involutional process that may have been occurring at that age. The rate of response, however, favors a response to therapy. Infantile hemangiomas involving the airway are difficult because the rate of growth during proliferation is unpredictable, and in the face of a child with stridor, apnea and feeding intolerance, conservative management is arduous. This is only made more difficult by the fact that most pediatric otolaryngologists see fewer than two cases of hemangiomas of the airway each year [11].

Propranolol has been successful in the treatment of subglottic hemangiomas in other reports with dramatic responses with few known side effects [7–9]. As experience with propranolol becomes more extensive across multiple institutions, it may become first line standard of therapy. However, it is far from clear how propranolol is best given: should it be tapered at onset? How long should therapy continue? Is there an optimal age of treatment? Is there benefit to concurrent systemic corticosteroid therapy? How should patients be monitored? What are the risks to children with cardiac and pulmonary co-morbidities? Is propranolol the best beta-blocker to use in this clinical scenario, or are there other beta-blockers with advantageous characteristics?

To date, propranolol at this dose (2 mg/kg/day divided three times a day) has been shown to be safe, but requires a long medical course with serial follow up and parent reliability. How does this compare to 1–2 surgical procedures for excision or debulking of focal lesions? Prednisolone has long been the gold standard in systemic therapy, but the systemic side effects of long-term therapy are well known, and many patients in previous reports required another modality of treatment. As further studies comparing prednisolone and propranolol reveal which is the safer and more efficacious drug, and more long-term data for propranolol is uncovered, it is important to incorporate surgical and medical alternatives to the treatment algorithm of these life threatening lesions.

In our series, all patients had a baseline EKG and blood pressure assessment prior to the initiation of propranolol. In our practice, it appears safe to be given on an outpatient basis, though it is recommended that the dose be gradually increased up to 2 mg/kg/day divided three times a day. As therapy may continue for several

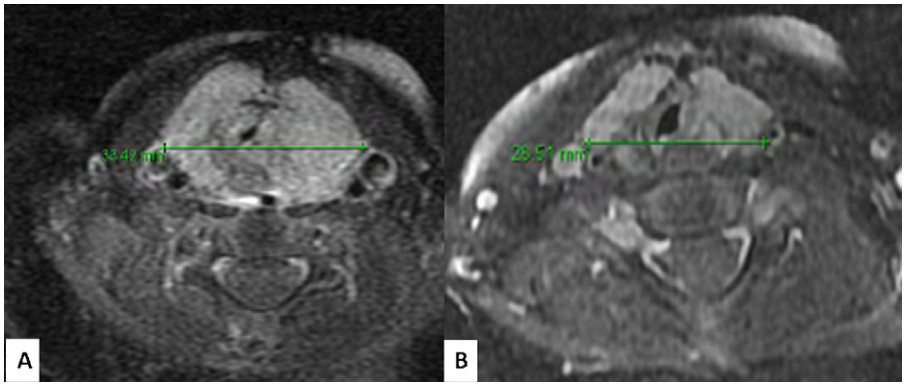

Fig. 4. Patient 6 axial imaging MRI at the level of the subglottis. Before propranolol therapy, hemangioma noted extending from subglottis to a circumferential lesion involving the thyroid gland, compressing the airway (A). After 1 week of propranolol therapy, significant improvement in subglottic airway and decreased size of circumferential extension (B).

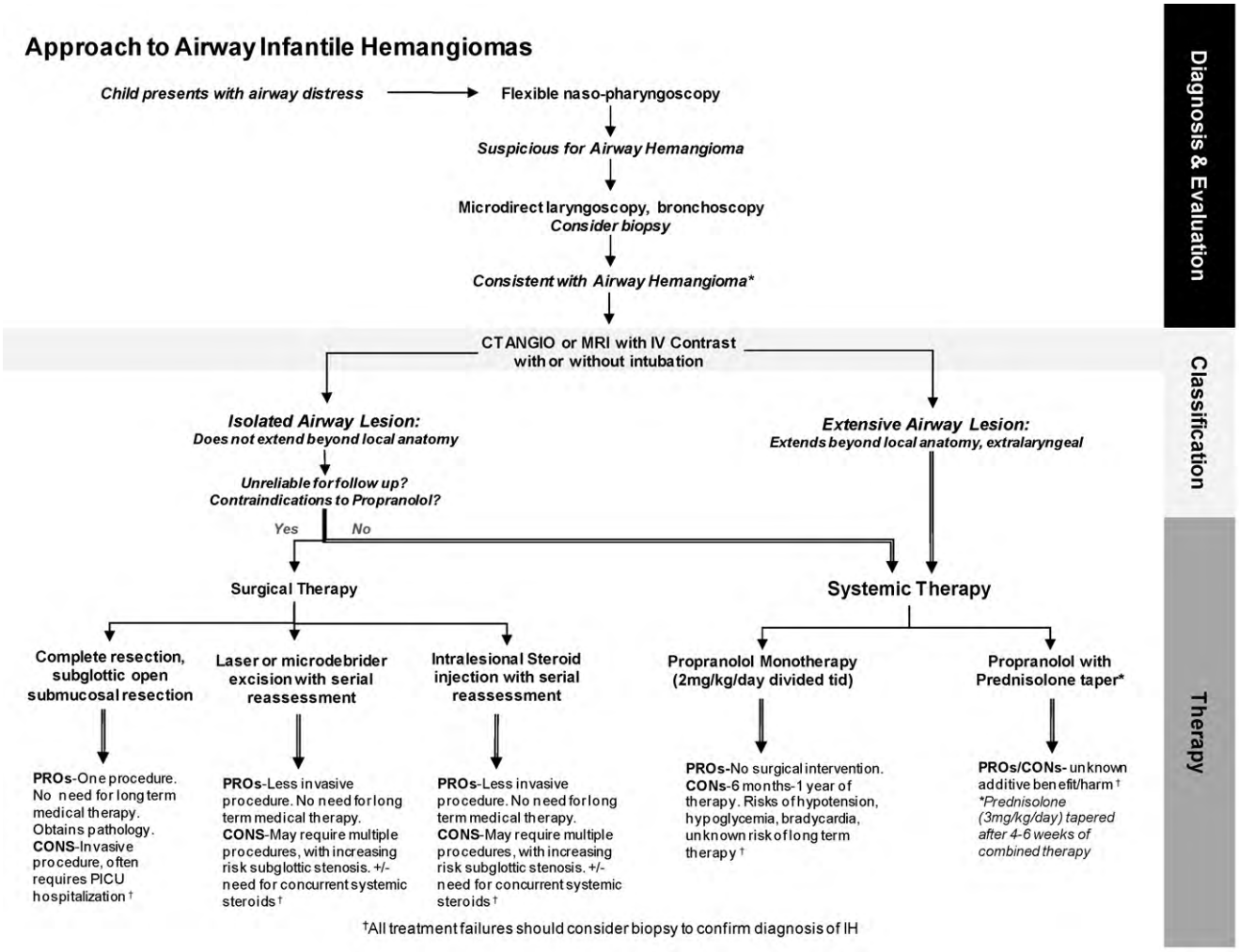

Fig. 5. Evaluation and treatment algorithm for airway hemangiomas.

months, the dose should be altered to account for the growth and weight gain of the child. With concerns for hypoglycemia, we have recommended giving doses with meals. Future studies will determine the importance of monitoring blood sugar throughout therapy. As the child is followed serially, symptoms and flexible nasopharyngoscopy may be used to assess the progress of the child. At approximately 6 months of treatment, we pursued a slow wean over approximately 2 weeks, allowing for the treatment to be restarted if symptoms were to return. Two patients initiated treatment later than age one, starting at 14 and 22 months.

Siegfried et al. recommended a baseline EKG and 48 h hospital stay or home nursing visits for blood pressure and glucose monitoring at initiation of therapy. The authors also recommended a starting dose of 0.16 mg/kg/dose every 8 h, and incrementally doubling to a final dose of 0.67 mg/kg/dose (equivalent to 2 mg/kg/day) [12,13]. This regimen was not utilized in this series as the initial experience with propranolol at each institution was prior to publication. In our practice, propranolol was safely given on an outpatient basis.

Propranolol is a non-specific beta adrenergic receptor blocker with hepatic metabolism. In its solution form, it has an elimination half-life of approximately 4 h. In the pediatric setting, propranolol has been prescribed for cardiac dysrhythmia, congestive heart failure, hypertension, Tetrology of Fallot, and thyroid storm. Propranolol is contraindicated in children bronchial asthma, cardiogenic shock, heart block (second and third degree), hypersensitivity to propranolol hydrochloride and sinus bradycardia. Precaution in administering propranolol is recommended in patients with bronchospastic lung disease, diabetes due to masked symptoms of hypoglycemia, hepatic impairment, renal impairment, thyrotoxicosis and Wolf–Parkinson–White syndrome [10].

It is not clear what percent of airway hemangiomas are truly focal or extend beyond the local anatomy [14]. However, it is important to distinguish the focal airway lesions from the lesions extending beyond the airway, limiting the efficacy of surgical treatment. After flexible nasopharyngoscopy and direct laryngoscopy, we are recommending considering imaging in the initial evaluation of airway hemangiomas, particularly when surgical treatments are being considered. Obtaining airway and neck imaging can be done without endotracheal intubation, though intubation may be required to secure the airway with sedation. If imaging is possible, obtaining a CT with intravenous contrast gives optimal tissue resolution of the hemangioma [14]. However, with concerns for radiation exposure to children with CT scans, an MRI/MRA with contrast can also be done. Imaging may also identify other occult hemangiomas, and is recommended in children with PHACE syndrome (Posterior fossa Hemangioma, Arterial lesions, Cardiac abnormalities/coarctation of aorta, Eye abnormalities). Confirmation of an extensive airway lesion leads the practitioner to favor systemic therapy. Factors such as parent reliability for long-term therapy, patient co-morbidities, and the potential for a few surgical procedures versus long-term medical regimens are considered in our algorithm (Fig. 5). As experience with

propranolol increases it may very well become the dominant therapy for even focal lesions. If this becomes the case, the added utility of routine imaging may then become more minimized other than to follow the progress of therapy.

However, when a patient does not appear to respond to therapy, or treatment fails, it is our opinion that a biopsy must be performed for pathology confirmation of the diagnosis of IH by histology and immunohistochemical staining for GLUT-1. Other proliferative vascular tumors besides infantile hemangiomas include pyogenic granulomas (lobular hemangiomas), tufted angiomas, kaposiform hemangioendotheliomas, rapidly involuting congenital hemangiomas (RICH), and non-involuting congenital hemangiomas (NICH) [2]. Only IH are GLUT-1 positive. We do not expect other vascular lesions other than IH to respond to propranolol, though the mechanism of this therapy is unknown.

Limitations to this study include the lack of standardization in medical therapies given, the small sample size, and the lack of post-treatment imaging or diagnostic procedures in all patients to confirm a reduction in size of IH. Prior to propranolol, there have been institutional philosophic differences in the treatment of IH. Despite differences in treatment and evaluation, propranolol has independently changed our respective institutions treatment paradigm.

5. Conclusions

We report a case series of seven patients treated with propranolol for hemangiomas of the airway. Six of seven patients with IH were treated successfully with propranolol despite failing systemic corticosteroids, intralesional steroids, and surgical management. The seventh patient required surgical resection of a tumor which was consistent with pyogenic granuloma on pathology. Infantile hemangiomas of the airway continue to be a difficult problem because of their unpredictability and the severity of symptoms. Evaluation of a patient suspected to have an airway hemangioma may include imaging to determine if the lesion is focal or extensive in deciding between medical and surgical management. Our exciting early experience leads us to conclude that propranolol will become an essential part of airway hemangioma management.

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