Propranolol Use for Infantile Hemangiomas

American Society of Pediatric Otolaryngology Vascular Anomalies Task Force Practice Patterns

Sanjay R. Parikh, MD; David H. Darrow, MD, DDS; J. Fredrik Grimmer, MD; Scott C. Manning, MD; Gresham T. Richter, MD; Jonathan A. Perkins, DO

**Importance:** This study provides multi-institutional practice guidelines for the initiation of propranolol hydrochloride treatment of routine infantile hemangiomas.

**Objective:** To provide information on current propranolol treatment practices for infantile hemangiomas among a cohort of pediatric otolaryngologists.

**Design and Setting:** A survey for initiation of propranolol therapy was created by the American Society of Pediatric Otolaryngology Vascular Anomalies Task Force Subcommittee. After an initial pilot of the survey by 4 task force members, the survey was modified and then distributed by e-mail. Results were transferred to spreadsheet format and analyzed.

**Participants:** All 51 members of the task force.

**Results:** A total of 18 respondents from 15 institutions submitted completed surveys. Data from respondents at the same institution were aggregated and/or averaged to minimize regional bias. Fourteen of 15 responding institutions (93%) treat patients with infantile hemangioma as part of a multidisciplinary vascular anomalies team. Ten institutions (67%) routinely consult cardiology before initiation of propranolol therapy. The median propranolol hydrochloride initiation dosage is 2.00 mg/kg/d (mean [SD], 1.65 [0.64]; range, 0.45-2.50 mg/kg/d. Post-initiation monitoring for propranolol therapy includes blood pressure (15 of 15 respondents [100%]), serum glucose levels (7 of 15 [47%]), and pulse oximetry (2 of 15 [13%]). Only 2 institutions routinely admit all patients for initiation of propranolol therapy. Typical duration of therapy ranges from 4 to 8 (5 of 15 [33%]) or 8 to 12 months (10 of 15 [67%]), and cessation of therapy in most cases is based on the clinical response (7 of 14 [50%]) or the age of the patient (6 of 14 [43%]).

**Conclusions and Relevance:** Propranolol is a commonly used medication for the treatment of infantile hemangiomas among otolaryngologists in the Vascular Anomalies Task Force. Propranolol therapy is commonly initiated in the outpatient setting and continued for as long as 12 months.

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**INFANTILE HEMANGIOMAS (IHS)** are benign vascular endothelial tumors that have a typical proliferative phase during infancy followed by an involution phase of variable duration. Complications of IH depend on the IH location and can be serious. These complications include airway compromise, vision loss, ulceration, heart failure, and death.

In 2008, Léauté-Labrèze et al described a series of 11 children with cervicofacial IH whose lesions were observed to respond to propranolol hydrochloride. Since that landmark description, propranolol has gained rapid popularity as the treatment of choice for IH. Léauté-Labrèze et al described using a propranolol hydrochloride dosage of 2.00 mg/kg/d in 3 divided doses. They also suggested that the mechanism of response was through downregulation of endothelial growth factors. Several proposed mechanisms of action include downregulation of angiogenesis, apoptosis of angiogenesis cell signaling, and vasoconstriction. The exact mechanism of action remains unknown.

Although propranolol has become widely popular as a medical therapy for IH, no consensus exists on indications, initiation workup, dosing, or safety. One report of a strategy for propranolol therapy initiation exists, which was multidisciplinary and largely outpatient based. In this report, all patients underwent a cardiology evaluation but were admitted for initiation only if they had known airway compromise, cardiac dysfunction, or predisposition to neurological compromise. Other reports of outpatient propranolol management have also been published.
to share experiences and discuss personal outcomes using different treatment modalities for vascular anomalies. Since 2008, propranolol has gained widespread acceptance within this group as an off-label therapeutic modality for IH. However, at a recent meeting of the task force, no strong consensus resulted regarding the principles for initiation and maintenance of propranolol therapy. We undertook the present survey of the task force members to gain insight into current propranolol therapy protocols among pediatric otolaryngologists.

Methods

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at a single institution. The REDCap system is a secure, web-based application designed to support data capture for research studies. It is hosted by Vanderbilt University (more information is available at http://www.project-redcap.org/). The tools provide (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources. Four task force members at 4 different institutions performed the initial pilot survey. Comments and suggestions were incorporated into a second revised survey that was sent to all task force members. Final survey data were exported to a spreadsheet (Excel; Microsoft Corp) from the REDCap software. Data were analyzed with descriptive statistics. Data from the same institutions were averaged to avoid institutional bias.

Results

Of the 51 task force members, a total of 18 respondents from 15 institutions submitted completed surveys (Table). Data from respondents at the same institutions were averaged so as to minimize regional bias, leaving 15 respondents for analysis. Fourteen respondents submitted complete surveys, and 1 respondent submitted a partial survey. Fourteen of the 15 institutions (93%) treat patients with IH as part of a multidisciplinary vascular anomalies team. Cardiology consultation is routinely sought in 10 of the 15 institutions (67%) before initiation of propranolol therapy (Figure 1). An electrocardiogram is obtained at 14 of the 15 institutions (93%) before commencing propranolol therapy. The median propranolol initiation dose is 2.00 (mean [SD], 1.65 [0.64]; range 0.45-2.50) mg/kg/d. Dosing intervals of propranolol are 2 times a day (7 of 15 respondents [47%]) or 3 times a day (8 of 15 [53%]). Postinitiation monitoring includes blood pressure (15 of 15 [100%]), serum glucose levels (7 of 15 [47%]), and pulse oximetry (2 of 15 [13%]) (Figure 2). Only 2 institutions routinely admit 100% of their patients for monitoring, whereas rates of admission vary among the other institutions (Figure 3). Typical duration of therapy ranges from 4 to 8 months (5 of 15 [33%]) or 8 to 12 months (10 of 15 [67%]) and rarely represented the main factor used to decide to stop therapy (1 of 14 [7%]; 1 survey was incomplete). Typical cessation of therapy is based on the clinical response (7 of 14 [50%]) or the age of the

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<th>Table. Participating Institutions</th>
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<td><strong>Institution</strong></td>
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<td>Arkansas Children’s Hospital</td>
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<td>The Johns Hopkins University</td>
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<td>Medical College of Wisconsin</td>
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<td>Morgan Stanley Children’s Hospital</td>
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<td>New York Eye and Ear Infirmary</td>
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<td>Oregon Health Sciences University</td>
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<td>Seattle Children’s Hospital</td>
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<td>The Hospital for Sick Children</td>
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Figure 1. Teams consulted as part of the protocol before initiation of propranolol hydrochloride therapy (response to “Which of the following providers do you routinely consult as part of workup for propranolol treatment?”).

The optimal dosing, timing, and duration of treatment remain unknown. Some reports have described rebound growth of hemangiomas after stopping propranolol therapy. Furthermore, reported response rates have ranged from 50% to 88%.

The safety profile of propranolol is largely based on pediatric experience for cardiovascular disease. As a nonselective β-blocker, the drug has the potential to cause bradycardia, bronchospasm, and/or hypotension. In addition, a risk of hypoglycemia exists, although the exact mechanism of action is not known.

In 2001, a group of American Society of Pediatric Otolaryngology (ASPO) members formed the ASPO Vascular Anomalies Task Force. This group of otolaryngologists from the United States and Canada meets twice a year to share experiences and discuss personal outcomes using different treatment modalities for vascular anomalies. Since 2008, propranolol has gained widespread acceptance within this group as an off-label therapeutic modality for IH. However, at a recent meeting of the task force, no strong consensus resulted regarding the principles for initiation and maintenance of propranolol therapy. We undertook the present survey of the task force members to gain insight into current propranolol therapy protocols among pediatric otolaryngologists.

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patient (6 of 14 [43%]). The first outpatient follow-up visit ranges from 3 to 30 days with a median of 7 days (Figure 4). The dosage reported as usually effective ranges from 2.00 mg/kg/d by 12 respondents to 2.50 and 3.00 mg/kg/d by 1 respondent each. The maximum dosage respondents are willing to administer are 2.00 (3 respondents), 2.50 (1 respondent), 3.00 (7 respondents), 4.00 (2 respondents), and 6.00 (1 respondent) mg/kg/d. The duration of propranolol therapy allowed for IH regression before the patient is deemed a nonresponder ranges from 2 to 12 weeks (Figure 5).

Among members of the ASPO Vascular Anomalies Task Force, propranolol has emerged as a common agent for IH treatment. Precise therapeutic indications, dosing, outcome measures, and the safety profile are yet to be determined. We initiated this survey to gain an understanding of the current treatment algorithms used by otolaryngologists treating IH. Although not designed to be a clinical practice guideline, this study acquaints interested clinicians with the variety of current treatment philosophies.

Propranolol therapy may be initiated on an inpatient or an outpatient basis. Our survey suggests that most centers (13 of 15) treat selected patients with uncomplicated disease courses on an outpatient basis. Only 2 of the 15 centers admit all patients for initiation of propranolol therapy. Although not specifically addressed in this study, many clinicians consider admission for infants younger than 2 months (or premature infants [<48 weeks after conception]), those with cardiovascular or respiratory comorbidities, those with disorders of glucose maintenance, and those whose caregivers may be unable to provide the necessary monitoring and support at home.

In this study, all 15 centers monitor blood pressure after the initiation of propranolol therapy, whereas fewer than half monitor blood glucose levels, electrocardiography, or pulse oximetry. Although we did not study respondents’ preferred time to initiate monitoring after starting propranolol therapy, many clinicians advocate giving the first outpatient dose and any dose increases in a setting in which heart rate and blood pressure may be checked 1 to 2 hours after administration. Adverse effects, such as bradycardia and hypotension, are usually
apparent after the initial dose, and we remain unclear on whether admission provides timelier and safer treatment of these adverse effects.

From this survey, we discovered that most of the responding institutions initiate propranolol hydrochloride therapy at a dosage of 2.00 mg/kg/d as initially described by Léauté-Labrèze et al. The ideal dosing interval remains unknown, but all study responders administer doses 2 or 3 times a day. Although the plasma half-life of propranolol is approximately 4 to 6 hours, its duration of action is 6 to 12 hours depending on the dose.

Although most IHs have completed 80% of their growth before the patient is 6 months of age, the proliferative growth phase may continue through the first year of life. As a result, some responders base the duration of therapy on patient age, whereas others use the patient’s clinical response. In addition, although systemic corticosteroid therapy is thought to be effective only during active proliferation of the hemangiomas, propranolol might be effective in other phases of the hemangioma growth cycle also. Termination of propranolol therapy may be appropriate once the proliferative phase is thought to be complete, with careful observation for evidence of additional growth. Because of the potential for rebound growth, tapering of therapy may be advisable. Our study could not establish whether the response to propranolol is dose-dependent.

As the primary strength of this study, we report the first survey of propranolol therapy initiation practices among otolaryngologists with a special interest in IH. Although the study is strictly descriptive, understanding current treatment practices across North America within a single specialty is of value. With a lack of control or statistical analysis, this study has an inherent weakness with regard to power and statistically based conclusions. In addition, our study had a low response rate that may be attributed to avoidance of redundant responses from the same institution, noncompletion of the survey by members who treat vascular anomalies other than hemangiomas, and/or disinterest in survey studies. As a whole, however, this survey allows us to conclude that propranolol is being used as the primary systemic therapy for IH within a narrow range for dose and frequency of therapy and that most institutions initiate such therapy on an outpatient basis for most of their patients.

In conclusion, propranolol is commonly used as medical therapy for the treatment of IHs among otolaryngologists in the ASPO Vascular Anomalies Task Force. To our knowledge, this is the first survey of the initiation of propranolol treatment practices for the management of IHs.

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Author Contributions: Drs Parikh, Richter, and Perkins 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: Parikh, Darrow, Grimmer, Manning, and Perkins. Acquisition of data: Parikh, Grimmer, and Richter. Analysis and interpretation of data: Parikh, Manning, Richter, and Perkins. Drafting of the manuscript: Parikh and Richter. Critical revision of the manuscript for important intellectual content: Parikh, Darrow, Grimmer, Manning, and Perkins. Statistical analysis: Parikh and Richter. Administrative, technical, and material support: Manning and Richter. Study supervision: Manning and Perkins.

Conflict of Interest Disclosures: None reported.

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REFERENCES