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CASE REPORT

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Efficacy and duration of propranolol therapy for pediatric parotid hemangiomas

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Abstract

Objective: *To assess the efficacy and duration of propranolol therapy in pediatric patients with parotid hemangiomas, and compare the results with the efficacy and duration of propranolol therapy in patients with infantile hemangiomas in other anatomic locations.*

Methods: *In this retrospective review, we analyzed the electronic medical records of 21 patients with parotid hemangiomas seen at the Children's Hospital of Orange County's Vascular Anomalies Clinic between 2009 and 2015. We compared the duration of propranolol therapy and rate of re-growth after completion of therapy with established data for these parameters in the literature for patients with other infantile hemangiomas.*

Results: *In our cohort, 13 of the 21 patients had completed therapy, with a mean duration of 26 months of propranolol therapy. Eighteen patients (85.7%) were treated with the goal dose of propranolol (2 mg/kg/day). Three patients required a higher dose in order to achieve significant improvement in the size of the hemangioma. All patients had some response to propranolol. Eight of the 13 patients (61.5%) who completed propranolol therapy saw regrowth once initial propranolol therapy was either weaned or stopped.*

Conclusion: *Pediatric patients with parotid hemangiomas require longer duration of propranolol therapy than patients with other infantile hemangiomas, and a greater percentage may have regrowth after completion of therapy.*

Keywords: *infantile hemangiomas, vascular, duration, regrowth*

Introduction

Infantile hemangiomas are benign, usually self-limited, tumors of vascular endothelium that are characterized by growth and involution phases [1]. Although most infantile hemangiomas are diagnosed clinically, imaging, and even tissue biopsy, may be needed to diagnose uncharacteristic, deeper lesions. Pediatricians often follow uncomplicated, localized hemangiomas with serial observation; however, medical therapy such as topical and systemic beta-blockers, and systemic and intralesional corticosteroids are available. The indications for treatment of complicated infantile hemangiomas can be divided into three categories: (1) ulceration, (2) disfigurement, and (3) impaired function of vital structures [2]. Oral propranolol is now the first-line agent for complicated hemangiomas, and used with good success [3-5]. A randomized controlled trial of oral propranolol versus placebo in proliferating infantile hemangiomas found that 88% of patients who received treatment showed improvement by the fifth week [6]. The majority of infantile hemangiomas are diagnosed in the head and the neck, followed by the trunk, and extremities. Of those on the head and the neck, parotid hemangiomas are specifically notorious for being more difficult to treat because of their propensity for expansive growth, resistance to treatment, and intimate relationship with the facial nerve [7].

Parotid hemangiomas are the most common benign salivary gland tumors in children, affecting girls three times more frequently than boys [8-10]. They typically are characterized by rapid growth in the first few months of life, with spontaneous regression around 18 months of age [11]. They can present as a focal lesion or as part of a segmental distribution. The more aggressive type is segmental with a prolonged growth phase and higher likelihood of associated ulceration, airway obstruction, and soft-tissue destruction [12]. Approximately 10% of parotid hemangiomas require medical intervention, and first line therapy is usually oral propranolol. Other therapeutic agents include intralesional corticosteroids, systemic corticosteroids, or interferon alfa-2a or -2b [12].One prior retrospective study of parotid hemangioma treatment found a 98% response to pharmacologic treatment with corticosteroids or interferon therapy after failure of corticosteroids. Their conclusion was that parotid hemangiomas respond to pharmacological treatment in a similar manner to hemangiomas in other locations. However, this study was prior to the widespread use of propranolol as first line therapy for parotid hemangiomas [13].

There are various case reports that demonstrate propranolol as an effective therapy for parotid hemangiomas [7,14], but, to our knowledge, there are no studies that specifically review the mean duration of propranolol therapy in treating parotid hemangiomas and outcomes after treatment completion. This study retrospectively assesses the efficacy of pharmacotherapy in patients with parotid hemangiomas referred to the Vascular Anomalies Center at The Children's Hospital of Orange County from 2009-2015, and also analyzes the mean duration of propranolol therapy required for these patients. We aim to compare the use of propranolol to treat parotid hemangiomas with hemangiomas of other anatomical locations.

Case presentation

Methods

Patients were referred to the Vascular Anomalies Center (VAC) at the Children's Hospital of Orange County by various practitioners, including otolaryngologists, general surgeons, plastic surgeons, dermatologists, and primary care physicians. The VAC is a collaborative clinic staffed by multiple specialists, including hematologists, otolaryngologists, plastic surgeons, laser surgeons, cardiologists, wound care specialists, and interventional radiologists. A diagnosis of parotid hemangioma is confirmed using ultrasound, computerized tomography scan, or magnetic resonance imaging of the head and neck area. Patients seen in the VAC with confirmed diagnoses of parotid hemangiomas are then evaluated for propranolol therapy. If deemed appropriate, they are started on an initial propranolol dosage of 0.5-1 mg/kg/day divided into twice per day dosing, with the eventual goal of increasing to a goal dose of 2 mg/kg/day divided twice per day. Prior to initiation of propranolol therapy, each patient requires completion of an electrocardiogram, echocardiogram, and clearance by a cardiologist. Patients with hemangiomas in a segmental distribution or patients with obstructive airway symptoms are evaluated by an otolaryngologist to assess for airway involvement with hemangioma, including subglottic hemangioma.

IRB approval was obtained for a retrospective chart review for patients with parotid hemangiomas seen at the VAC. We evaluated for duration of treatment until complete resolution of the lesion, along with adjunct treatment modalities and complications. Patients included in the study had either completed propranolol therapy or were currently undergoing treatment. Patients who had initiated propranolol treatment and were lost to follow up were also included for analysis.

Results

Of the 21 patients with parotid hemangiomas included in this analysis, 33.3% were male and 66.7% were female (Table 1). The majority of our study population identified as Hispanic White (47.6%). Mean age of presentation was 2.15 months, with a range of two weeks to five months. 85.7% were born at full term, and 90.5% were the result of a singleton pregnancy. 19% had complications during pregnancy and/or delivery: IUGR (one patient), breech positioning (one patient), nuchal cord (one patient), and subchorionic hemorrhage (one patient). 10 patients (47.6%) presented with a left cheek and parotid gland hemangioma, nine (42.9%) with a right cheek and parotid gland hemangioma, two (9.5%) with bilateral parotid hemangiomas, and three (14.3%) with a beard distribution lesion (Table 2). 13 patients (61.9%) had completed therapy at the time of this analysis, with a mean duration of 25.8 months and range of five to 48 months. Four patients were lost to follow-up. Four patients remained on treatment at the time of this analysis. 18 patients (85.7%) were treated with the goal dose of propranolol (2 mg/kg/day); however three patients required a higher dose in order to achieve significant improvement in the size of the hemangioma. Two patients (9.5%) required a maximum dose of 3 mg/kg/day, and one patient (4.8%) required a maximum dose of 4 mg/kg/day. There were no patients treated below the goal dose of 2 mg/kg/day, and all patients had some response to propranolol. Eight of the 13 patients (61.5%) who completed propranolol therapy saw regrowth once initial propranolol therapy was either weaned or stopped. Three patients (14.3%) received concomitant steroid therapy in the early phase because of airway involvement. Two patients (9.5%) required tracheostomy to maintain airway patency, two (9.5%) required surgical resection, and one (4.8%) required laser therapy. Upon review of the screening echocardiogram, 13 patients (61.9%) were found to have positive findings. The findings included one or more of the following: left ventricular hypertrophy (two patients, 15.4%), patent foramen ovale (nine patients, 69.2%), ventricular septal defect (two patients, 15.4%), dilated left ventricle (one patient, 4.8%), and functional bicuspid aortic valve (one patient, 4.8%).

Discussion

The majority of our study population was female which is consistent with previously reported demographic profiles for infantile hemangiomas [8]. The mean duration of propranolol therapy for the 13 patients who completed therapy in this analysis was 25.8 months, which is significantly longer than the average duration of treatment of six to nine months for infantile hemangiomas in general as described in the literature. A multicenter, randomized, double-blind, controlled trial of oral propranolol in patients with infantile hemangiomas in all locations using a dose of propranolol of 3 mg/kg/day described 60% complete resolution by 6 months [6]. Another study also found an effective mean duration of 6 months of propranolol therapy for their 55 patients

	Total (n=21)
Sex	
Male	7 (33.3%)
Female	14 (66.7%)
Race	
Hispanic White	10 (47.6%)
Non-Hispanic White	3 (14.3%)
Asian	3 (14.3%)
African-American or Black	1 (4.8%)
Unknown	4 (19.0%)
Gestational Age	
Full term (>37 weeks)	18 (85.7%)
Preterm (<37 weeks)	3 (14.3%)
Singleton Pregnancy	
Yes	19 (90.5%)
No (Twin Pregnancy)	2 (9.5%)
Complications during pregnancy	
Yes	4 (19.0%)
No	17 (81.0%)
Positive echocardiogram findings	
Yes	13 (61.9%)
No (normal echocardiogram)	8 (38.1%)
Positive echo findings	
Left Ventricular Hypertrophy	2 (15.4%)
Patent Foramen Ovale	9 (69.2%)
Ventricular Septal Defect	2 (15.4%)
Other	2 (15.4%)

Table 1. *Demographic information of study population.*

Patient	Age at initial presentation	Location of hemangioma	Duration of treatment	Dose of propranolol	Other treatments	Complications
1	3 weeks	Left parotid gland, beard distribution, airway hemangioma	37 months	4 mg/kg/day	Tracheostomy	Airway obstruction
2	2 weeks	Beard distribution, airway, bilateral parotid glands, anterior chest wall	39 months	3 mg/kg/day	Steroids (2 months), Tracheostomy	Airway obstruction, Ulceration
3	1 month	Right cheek and parotid gland	20 months	3 mg/kg/day	None	None
4	2 months	Left parotid gland, posterior part of left ear	48 months	2 mg/kg/day	Surgical resection	Regrowth when medication weaned, Ulceration
5	2 months	Right cheek and parotid gland	32 months	2 mg/kg/day	Steroids (2months)	Regrowth when medication weaned
6	1 month	Right parotid gland	32 months	2 mg/kg/day	None	None
7	2 weeks	Right parotid gland and right periorbital region	31 months	2 mg/kg/day	None	Regrowth when medication weaned
8	2.5 months	Left cheek and parotid gland	28 months	2 mg/kg/day	Steroids (2 months)	Regrowth when medication weaned
9	1 month	Left cheek and parotid gland	20 months	2 mg/kg/day	None	None
10	1 month	Bilateral cheeks and parotid glands, neck, and beard distribution	16 months	2 mg/kg/day	Laser	None
11	2 months	Right parotid gland, right cheek, and back of neck	15 months	2 mg/kg/day	None	Regrowth when medication weaned
12	1 months	Left neck and parotid gland	12 months	2 mg/kg/day	Surgical resection	Regrowth when medication weaned
13	5 months	Right cheek, abutting right parotid gland	5 months	2 mg/kg/day	None	Regrowth when medication weaned
14	2.5 months	Left cheek and parotid gland	20 months (ongoing)	2 mg/kg/day	None	Regrowth when medication weaned
15	4 months	Left cheek and parotid gland	12 months (ongoing)	2 mg/kg/day	None	None
16	3 months	Left cheek, abutting , left parotid gland	6 months (ongoing)	2 mg/kg/day	None	None
17	5 months	Left cheek and parotid gland	3 months (ongoing)	2 mg/kg/day	None	None
18	2 months	Left cheek and parotid gland	15 months until lost to follow-up	2 mg/kg/day	None	Unknown as lost to follow-up
19	4 months	Right cheek and parotid gland	9 months until lost to follow-up	2 mg/kg/day	None	Unknown as lost to follow-up
20	2 months	Right parotid gland, and orbital and facial areas	3 months until lost to follow-up	2 mg/kg/day	None	Unknown as lost to follow-up
21	4 months	Right cheek and parotid gland	2 months until lost to follow-up	2 mg/kg/day	None	Unknown as lost to follow-up

Table 2. *Characteristics of study population.*

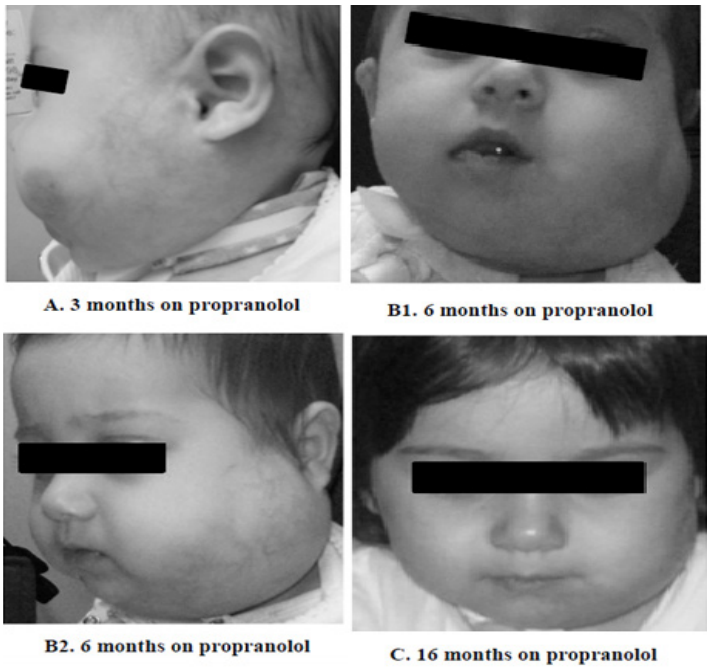

Figure 1. *Progression of parotid hemangioma in Patient 1. She presented at 3 weeks of age with the finding of left parotid gland hemangioma with airway involvement, requiring tracheostomy. Duration of treatment was 37 months, with a maximum propranolol dose of 4 mg/kg/day.*

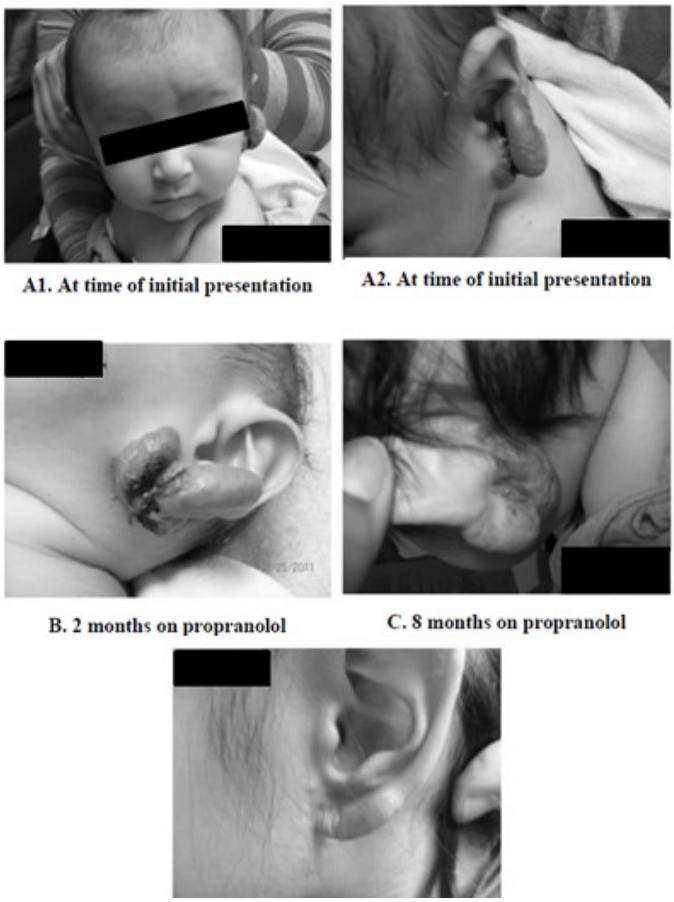

Figure 2. *Progression of parotid hemangioma in Patient 4. She presented at 2 months of age with the finding of left parotid gland hemangioma extending to the posterior part of the left ear. She required surgical resection of the portion on the left ear. Duration of treatment was 48 months, with a maximum propranolol dose of 2 mg/kg/day.*

with various types of infantile hemangiomas [15]. 61.5% of our study population had rebound growth approximately 12 to 18 months after completing therapy, versus approximately 10 to 15% described in the other studies [6,16,17]. All of the patients in our study population were responsive to propranolol therapy (Figures 1 and 2). Other studies have found that approximately 0.9 to 1.8% of patients with infantile hemangioma do not have improvement with propranolol treatment [15,18].

Our study has shown that parotid hemangiomas have a longer proliferative phase, that these patients need a longer treatment course, and have a higher relapse rate. One limitation of our study is the relatively small sample size. Further prospective analyses of larger cohorts of children with parotid hemangiomas should be conducted to verify the duration of therapy to complete resolution. The majority of our patients also identified as Hispanic White, potentially limiting the generalizability of our findings. However, regardless of these limitations, the information from out study will help in determining the treatment course of these lesions, as well as counseling parents on the importance of compliance with medication and incidence of recurrence if treatment is stopped early. Future trials with a higher goal dose of propranolol (3 mg/kg/day) in patients who are diagnosed with parotid hemangiomas may be considered to attempt to shorten the proliferative phase of these lesions. Pre-treatment biopsies are rarely performed on these lesions, but may be considered in an attempt to explain the biological basis of the prolonged proliferative phase observed in parotid hemangiomas. As has been established by prior studies, there are multiple biologic markers that characterize the individual phases of infantile hemangiomas, including vascular endothelial grown factor (VEGF), basic fibroblast growth factor (bFGF), tissue inhibitor metalloproteinases (TMP), and glucose transporter type 1 (GLUT-1) [19]. Analyses of specific biologic markers would give valuable information that would help the scientific community better understand why parotid hemangiomas require longer length of treatment compared to non-parotid hemangiomas. Lastly, many of the patients in our cohort had a positive echocardiogram finding, but these findings did not preclude them from initiation of propranolol therapy or from tolerating it well. Further data analyzing the long-term safety of propranolol in patients with abnormal echocardiograms would be valuable in creating future care guidelines for the treatment of parotid hemangiomas.

References

1. Darrow DH, Greene AK, Mancini AJ, Nopper AJ. Diagnosis and management of infantile hemangioma. *Pediatrics.* 2015; 136:e1060-e104.
2. Luu M, Frieden IJ. Haemangioma: clinical course, complications and management. *Br J Dermatol.* 2013; 169:20-30.
3. Schiestl C, Neuhaus K, Zoller S, Subotic U, Forster-Kuebler I, et al. Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas. *Eu J of Peds.* 2011; 170:493-501.
4. Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. *Pediatr Dermatol.* 2013; 30:182-191.
5. Holmes WJM, Mishra A, Gorst C, Liew SH. Propranolol as first-line treatment for rapidly proliferating infantile haemangiomas. *JPRAS.* 2011; 64:445-451.
6. Leaute-Labreze C, Hoeger P, Mazereeuq-Hautier J, Guibaud L, Baselga E, et al. A randomized, controlled trial of oral propanolol in

infantile hemangioma. *N Engl J Med.* 2015; 372:735-746.
7. Weiss I, O TM, Lipari BA, Meyer L, Berenstein A, et al. Current treatment of parotid hemangiomas. *Laryngoscope.* 2011; 121:1642-1650.
8. Roebuck DJ, Ahuja AT. Hemangioendothelioma of the parotid gland in infants: sonography and correlative MR imaging. *Am J Neuroradiol.* 2000; 21:219-223.
9. Brandling-Bennett HA, Metry DW, Baselga E, Lucky AQ, Adams DM, et al. Infantile hemangiomas with unusually prolonged growth phase: a case series. *Arch Dermatol.* 2008; 144:1632-1637.
10. Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics.* 2006; 118:882-887.
11. Tuna IS, Doganay S, Yikilmaz A, Coskun A. Hemangioma of the parotid gland in an infant: MR and doppler US findings. *Eurasian J Med.* 2009; 41:141.
12. Qureshi NA, Singhal J, Sharma J. Parotid gland hemangioma. *Indian Pediatrics*. 2013; 50:1071-1072.
13. Greene AK, Rogers GF, Mulliken JB. Management of parotid hemangioma in 100 children. *Plast Reconstr Surg.* 2004; 113:53-60.
14. Mantadakis E, Tsouvala E, Deftereos S, Danielides V, Chatzimichael A. Involution of a large parotid hemangioma with oral propranolol: an illustrative report and review of the literature. *Case Reports in Peds.* 2012; 12.
15. Schupp CJ, Kleber J-B, Günther P, Holland-Cunz S. Propranolol therapy in 55 infants with infantile hemangioma: dosage, duration, adverse effects, and outcome. *Pediatr Dermatol.* 2011; 28:640-644.
16. Shah SD, Baselga E, McCuaig C, Pope E, Coulie J, et al. Rebound growth of infantile hemangiomas after propranolol therapy. *Pediatrics*. 2016; 137: e20151754.
17. Wedgeworth E, Glover M, Irvine AD, Neri I, Baselga E, et al. Propranolol in the treatment of infantile haemangiomas: lessons from the European propranolol in the treatment of complicated haemangiomas (PITCH) taskforce survey. *Br J Dermatol.* 2016; 174:594-601.
18. Caussé S, Aubert H, Saint-Jean M, Puzenat E, Bursztejn AC, Eschard C, et al. Propranolol-resistant infantile haemangiomas. *Br J Dermatol.* 2013; 169:125.
19. Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol.*

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