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Effectiveness of Propranolol in the Treatment of Infantile Hemangioma Beyond the Proliferation Phase

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Abstract: **During the last 5 years, many studies have shown the efficacy of propranolol as first-line treatment for infantile hemangiomas (IHs), but not much has been written about the role of propranolol beyond the proliferation phase of IH (>1 year). Our aim was to assess propranolol efficacy and safety in the treatment of patients older than 1 year. A retrospective study of patients older than 1 year diagnosed with IH and treated in our vascular anomalies clinic between 2009 and 2013 was performed. Eighteen patients older than 1 year with a diagnosis of IH (15 girls, 3 boys) were identified. The mean age at the time of initiation of treatment was 25.7 months (range 13–72 mos). Single lesions were observed in 13 patients and multiple lesions in 5. Fifteen patients had focal lesions and three had segmental. The median duration of treatment with oral propranolol was 11.8 months (range 2–33 mos). Complete response was observed in 72.2% of the patients and partial response in 27.8%. Recurrence was observed in three patients 4.7 months after completion of therapy (range 0.3–8 mos). These patients required further therapy with propranolol for 6 more months. Bradycardia was documented in two patients and night terrors in one patient, which led to discontinuation of treatment. In our experience, propranolol may be useful in the treatment of IHs beyond the proliferation phase (>1 year old), but more studies are needed to support this observation.**

Infantile hemangiomas (IHs), which are characterized by endothelial cell hyperproliferation, are the most common soft tissue tumors of infancy. They occur in 4% to 10% of children younger than 1 year of age, with a female predominance (1,2). Most hemangiomas become evident within the first few weeks of life and may be subtle at birth, after which they enter a phase of rapid growth lasting from 3 to 6 months (3). A period of stabilization for a few months follows, with spontaneous involution, which

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usually takes 3 to 7 years (4). High endothelial immunoreactivity for the erythrocyte-type glucose transporter protein (GLUT1) is a specific feature of IHs during all phases of these lesions and has become a useful marker for diagnosis (5).

Although IHs are usually asymptomatic, some may cause significant morbidity, including ulceration, visual impairment, airway compromise, and significant disfigurement. For decades, therapeutic options for complicated IHs have included systemic and intralesional steroids, interferon, vincristine, lasers, and surgical excision (6,7).

In 2008, Leauté-Labrèze et al (8) reported a series of 11 cases in which oral propranolol, a nonselective beta-blocker, dramatically improved the color and texture of severe or disfiguring IHs. The exact mechanism of action of propranolol is unclear but may involve microvascular vasoconstriction and modulation of angiotensin II (9). Alterations in the cell signaling of angiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor, and metalloproteinases and early apoptosis of endothelial cells may also be involved (10–12).

Since Leauté-Labreze et al's description, other authors have reported similar observations, although most discuss the efficacy of propranolol during the proliferative phase of IH. The growth cycle is typically divided into early, late proliferative, and involution stages, but the duration of these stages can vary between IHs subtypes (superficial, deep, mixed) (13).

The growth characteristics of IHs were rigorously evaluated in a large prospective study that found the early proliferative growth phase was essentially complete by 3 months of age and overall growth was nearly always complete before 5 months of age (3,14). Although only a small proportion of IHs grow after 5 months of age, their continued growth can cause therapeutic challenges, functional sequelae, and considerable parental anxiety (13).

Our aim was to assess propranolol efficacy and safety in the treatment of patients older than 1 year.

MATERIALS AND METHODS

A retrospective study of patients older than 1 year with a diagnosis of IH evaluated and treated in a vascular anomalies clinic in a tertiary pediatric hospital between 2009 and 2013 was performed.

Variables analyzed included age at initiation of treatment, sex, lesion location, number of lesions, distribution, depth of lesion, duration of treatment, adverse reactions, and response rate to propranolol.

Before outpatient treatment initiation, an electrocardiogram, blood pressure and heart rate monitoring, and serum glucose level were performed in all patients.

Patients were assessed 3, 6, 9, 18, 24, 30, and 36 months after initiation of treatment. Criteria for therapy response included a decrease in the intensity of color and volume. Response was defined as absent (the lesion continued growing), stable (maintenance or minimal reduction of volume or clearance), partial (partial volume reduction and clearance), or complete (total clearance and flattening or only residual telangiectasia).

RESULTS

Table 1 lists the clinical characteristics, treatment, and outcomes of the patients. From 2009 to 2013, 18 patients older than 1 year with a diagnosis of IH were treated with propranolol at a dose of 2 mg/kg/day (divided into two doses). Five patients received up to 4 mg/kg/day.

Fifteen girls and three boys with a mean age of 25.7 months (range 13–72 mos) at the time of treatment initiation were identified. Single lesions were observed in 13 patients and multiple lesions in 5. Fifteen patients had focal lesions and three had segmental lesions. The most common lesion site was craniofacial (n = 14 [73.6%]). Seventeen patients had mixed lesions (superficial and deep components) (Fig. 1) and one had a deep lesion (Fig. 2). Before propranolol treatment, 10 patients had received no therapy, 3 were treated with corticosteroids, 4 had partial surgical resection, and 1 had undergone laser treatment. The median duration of treatment with propranolol was 11.8 months (range 2–33 mos). Complete response was observed in 72.2% of the patients and partial in 27.8%. Recurrence was observed in three patients 4.7 months after completion of therapy (range 0.3–8 mos). These patients required therapy with propranolol for 6 more months. Three patients had side effects (bradycardia in two, night terrors in one) that led to discontinuation of treatment. Two of these patients had a complete response and one had a partial response at the time of discontinuation of propranolol therapy. Both patients (ages 14 and 25 mos) who experienced bradycardia during propranolol therapy were treated at a dose of 2 mg/kg/day. The first patient had a complete response (duration of treatment 2 mos) and the second had a partial response (duration of treatment 6 mos). Bradycardia was noted in a routine follow-up visit in both cases.

TABLE 1. *Epidemiologic Data and Response to Oral Propranolol of Patients Older Than 1 Year with Infantile Hemangiomas*

Sex	Age, months	Lesion location	Prepropranolol therapy	Duration of propranolol therapy, months	Response
Female	14	Mandible	None	2	Complete
Female	25	Cheek, leg, helix	None	6	Partial
Female	78	Lip	Laser	10	Partial
Female	18	Back	None	3	Partial
Female	22	Eyelid	None	33	Complete
Female	24	Lip	None	10	Complete
Female	14	Neck	Corticosteroids	11	Complete
Female	18	Pinna	None	11	Complete
Female	37	Pinna	Surgery	12	Partial
Male	13	Scrotum, front	Surgery	13	Complete
Female	13	Eyelid, lumbar	Surgery	16	Complete
Female	17	Nose	Corticosteroids	16	Complete
Female	33	Lumbar, scalp	Surgery	20	Complete
Male	19	Nose	None	6	Complete
Female	26	Scalp, abdomen	None	7	Complete
Female	23	Elbow	Corticosteroids	10	Partial
Female	48	Chin	None	12	Complete
Male	22	Lip	None	16	Complete

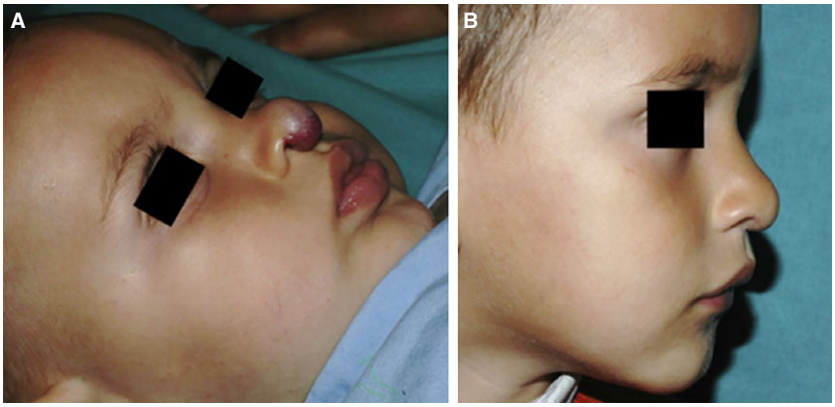

Figure 1. Mixed (superficial and deep) infantile hemangioma of the nasal tip (**A**) before propranolol at the age of 18 months and (**B**) after propranolol at the age of 34 months.

Patients (n = 5) who received up to 4 mg/kg/day did not respond to lower doses. Lesions were located on the upper eyelid (n = 2), nasal tip (n = 1), shoulder (n = 1), and lower lip (n = 1). The median duration of treatment with propranolol was 7.2 months (range 7–9 mos). No side effects were observed. Complete response was documented in all the lesions except for one, which was ulcerated before therapy.

DISCUSSION

Approximately 10% of IHs require treatment during the proliferative phase because of life-threatening location, local complications, or cosmetic or functional risks (15). In 2008 Léauté-Labréze et al (8) reported the incidental finding that propranolol could efficiently control the growth of IHs. Other studies conducted since then have shown excellent effect and good tolerance (16). Within hours of starting therapy, propranolol produces vasoconstriction, resulting in a reduction in the color of the hemangioma. Schneider et al (17) state that this involution seems not to depend on the location of the hemangioma or the age at initiation of therapy, although most authors agree that a good response is expected when the therapy is started within the first 12 months of life. Razon et al (18) demonstrated that the involutive phase of IH involves high apoptosis and proliferation of endothelial cells and concluded that increased apoptosis during the second year of life can offset cellular proliferation and may be involved in initiating the regression of hemangiomas.

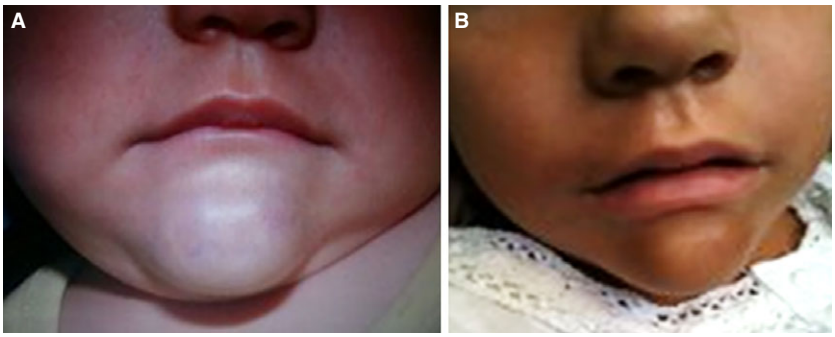

Figure 2. Deep infantile hemangioma of the chin (**A**) before propranolol at the age of 13 months and (**B**) after propranolol at the age of 5 years.

Our aim was to assess the efficacy and safety of propranolol in the treatment of patients older than 1 year since there are not many articles in the medical literature in which the effectiveness of propranolol beyond the proliferation phase is discussed. Zvulunov et al (19) recently studied a series of 42 patients diagnosed with IH treated with propranolol beyond the proliferation phase. The mean propranolol dose used was 2.1 mg/kg/day (range 1.5–3 mg/kg/day), and they concluded that propranolol is uniquely effective in IH, including in the postproliferative phase, and should be considered as first-line therapy in that setting.

The duration of treatment with systemic propranolol ranges from 1 to 16 months in the current literature (20–22). In our study group, a complete response was observed in 72.2% of cases and a partial response in 27.7%, with a mean duration of treatment of 11.8 months (range 2–33 mos), although a variable rebound rate in some lesions is described after completion of propranolol therapy (23–26). Schneider et al (17) observed a rebound rate of 12.1%, with an indication for a second propranolol therapy regimen in 7.7% of the patients. Khan et al (27) isolated CD133 hemangioma stem cells from proliferating-phase IHs using anti-YCD133-coated magnetic beads, and their findings provide evidence of a stem cell origin of IHs, which is in contrast to the long-held view that IHs arise from endothelial cells. Wong et al (28) assumed that hemangioma stem cells continue to proliferate albeit at a slow rate in IHs, which could explain the phenomenon of rebound growth after propranolol therapy has been tapered. In our series, lesion recurrence was observed in three patients that required 6 more months of propranolol treatment, achieving a complete response after that time.

Although propranolol is considered to be well tolerated and associated with limited adverse reactions, it should be used with caution for the first several doses because of the chance of potential side effects, including bradycardia, hypotension, fatigue, bronchospasm, and hypoglycemia (29,30). Oral propranolol was administered to our patients only after meals, which may be helpful in avoiding hypoglycemia. Bradycardia was documented in two patients and night terrors in one, which led to discontinuation of treatment and disappearance of the side effects. No recurrence of the lesions was observed.

Some limitations of this retrospective study should be highlighted. There were a small number of subjects (n = 18), and it is difficult to determine associations between treatment duration and the type and location of the hemangioma. Further studies are needed to investigate the relationship between the duration of treatment and lesion type beyond the proliferation phase.

In conclusion, the use of oral propranolol is well tolerated, effective, and safe in the treatment of IHs beyond the proliferation phase (>1 year of age), although more studies are needed to confirm this observation.

REFERENCES

1. Frieden IJ, Haggstrom A, Drolet BA et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas. Pediatr Dermatol 2005;22:383–406.
2. Bruscino N, Bonan P, Cannarozzo G et al. Laser use in infantile hemangiomas, when and how. Dermatol Ther 2012;25:314–321.
3. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med 1999;341:173–181.
4. Maguiness SM, Frieden IJ. Vascular birthmarks: tumors and malformations. In: Schachner LA, Hansen RC, eds. Pediatric dermatology, vol. 2, 4th ed. Philadelphia: Mosby Elsevier, 2011:1135–1153.
5. North P, Waner M, Mizeracki A et al. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 2000; 31:11–22.

6. Perkins JA, Oliaei S, Garrison MM et al. Airway procedures and hemangiomas: treatment patterns and outcome in U.S. pediatric hospitals. Int J Pediatr Otorhinolaryngol 2009;73:1302–1307.
7. Perkins JA, Duke W, Chen E et al. Emerging concepts in airway infantile hemangioma assessment and management. Otolaryngol Head Neck Surg 2009;141:207–202.
8. Leauté-Labrèze C, de la Roque ED, Hubiche T et al. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008;358:2649–2651.
9. Itinteang T, Brasch HD, Tan ST et al. Expression of components of the renin-angiotensin system in proliferating infantile haemangioma may account for the propranolol-induced accelerated involution. J Plast Reconstr Aesthet Surg 2010;64:759–765.
10. Leauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: part II. Risks, complications and treatment. J Eur Acad Dermatol Venereol 2011;25:1254–1260.
11. Iaccarino G, Ciccarelli M, Soriento D et al. Ischemic neoangiogenesis enhanced by beta2-adrenergic receptors overexpression: a novel role for the endothelial adrenergic system. Circ Res 2005;97:1182–1189.
12. Frieden IJ, Drolet BA. Propranolol for infantile hemangiomas: promise, peril, pathogenesis. Pediatr Dermatol 2009;26:642–644.
13. Chang LC, Haggstrom AN, Drolet BA et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008;122:360–367.
14. Bernabeu-Wittel J, Pereyra-Rodríguez JJ, Mantrana-Bermejo ME et al. Propranolol for the treatment of severe hemangiomas of infancy: results from a series of 28 patients. Actas Dermosifiliogr 2011;102:510–516.
15. Enjolras O, Gelbert F. Superficial hemangiomas: associations and management. Pediatr Dermatol 1997;14:173–179.
16. Schiestl C, Neuhaus K, Zoller S et al. Efficacy and safety of propranolol as first-line treatment for infantile hemangiomas. Eur J Pediatr 2010;124:423–431.
17. Schneider M, Cremer H, Ruef P. A retrospective analysis of systemic propranolol for the treatment of complicated infantile haemangiomas. Acta Paediatr 2014;103:977–983.
18. Razon MJ, Kraling BM, Mulliken JB et al. Increased apoptosis coincides with onset of involution in infantile hemangioma. Microcirculation 1998;5:189–195.
19. Zvulunov A, McCuaig C, Frieden IJ et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study. Pediatr Dermatol 2011;28:94–98.
20. Izadpanah A, Kanevsky J, Belzile E et al. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. Past Reconstr Surg 2013;131:601–613.
21. De Graaf M, Breur JM, Raphael MF et al. Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants. J Am Acad Dermatol 2011;65:320–327.
22. Sans V, Dumas de la Roque E, Berge J et al. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009;124:423–431.
23. Drolet BA, Frommelt PC, Chamlin S et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013;131:128–140.
24. Bagazgoitia L, Torrelo A, Gutierrez JC et al. Propranolol for infantile hemangiomas. Pediatr Dermatol 2011;28:108–114.
25. Jin Y-b, Lin X-x, Ye X-x et al. A prospective study of propranolol as first-line treatment for problematic infantile hemangioma in China [in Chinese]. Zhonghua Zheng Xing Wai Ke Za Zhi 2011;27:170–173.
26. Zaher H, Rasheed H, Hegazy RA et al. Oral propranolol: an effective, safe treatment for infantile hemangiomas. Eur J Dermatol 2011;21:558–563.
27. Khan ZA, Boscolo E, Picard A et al. Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. J Clin Invest 2008;118:2592–1599.
28. Wong A, Hardy KL, Kitajewski AM et al. Propranolol accelerates adipogenesis in hemangioma stem cells and causes apoptosis of hemangioma endothelial cells. Plast Reconstr Surg 2012;130:1012–1021.
29. Holland KE, Frieden IJ, Frommelt PC et al. Hypoglycemia in children taking propranolol for the treatment of infantile hemangioma. Arch Dermatol 2010;146:775–778.
30. Bonifazi E, Acquafredda A, Milano A et al. Severe hypoglycemia during successful treatment of diffuse hemangiomatosis with propranolol. Pediatr Dermatol 2010;27:195–196.