Expanding Uses of Propranolol in Dermatology

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Propranolol as a dermatologic therapeutic tool was first described in 2008. Since then, propranolol has had a pivotal role in the dermatology arena for a myriad of cutaneous disorders. This article highlights the timeline of the incorporation of propranolol as a treatment option for a number of vascular lesions.

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Since the serendipitous discovery of expedited involution of infantile hemangiomas (IHs) with propranolol in 2008,[1] current research has proliferated to discern the mechanism of action of beta-blockers in the care of IHs. Propranolol is a nonselective beta-blocker with a structure similar to catecholamines and thus competes for β-adrenergic receptors. Blocking β_1-receptors is cardioselective, leading to decreased heart rate and myocardial contractility, while blocking β_2-receptors leads to inhibition of smooth muscle relaxation and decreased glycogenolysis. The endothelial cells of IH express β_2-adrenergic receptors; the mechanistic role of propranolol in these lesions is surmised to be due to vasoconstriction, decreased angiogenesis through inhibition of vascular endothelial growth factor, and subsequent endothelial cell apoptosis.[2]

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After this breakthrough finding, a subsequent novel development was made when an ophthalmologist demonstrated that timolol, a topical beta-blocker, could be utilized to expedite IH involution and prevent ocular complications such as amblyopia secondary to the mass effect of the lesion. Guo and Ni[3] prescribed the commercially available ophthalmologic solution of timolol maleate 0.5% for twice-daily use for 5 weeks. Remarkable reduction in the periorbital IH without rebound phenomenon was observed.[3] A recent multicenter retrospective cohort of more than 700 patients with IH were treated with topical timolol with a 70% success rate, corresponding to 10% improvement from baseline; this study highlights the efficacy of timolol while confirming the safety of the medication.[4]

Systemic beta-blockers for IH have been used predominately for critical sites such as the nasal tip, lip, ear, perineum, and periocular area; ulcerated lesions or those that may be prone to leave a fibrofatty tissue residue after involution also have been targeted. Contraindications for use include premature infants younger than 5 weeks, infants weighing less than 2 kg, history of asthma or bronchospasm, heart rate less than 80 beats per minute, blood pressure less than 50/30 mm Hg, or hypersensitivity to the medication.[5] Current guidelines for propranolol initiation vary; some dermatologists consult cardiology prior to initiation, while others perform routine vitals and an indication-driven electrocardiogram as needed based on family history of cardiac disease, maternal history of connective tissue disease, congenital heart block, or abnormal vital signs.

Given the demonstrated long-term safety of propranolol and the acceptable side-effect profile, the use of beta-blockers for IH has become increasingly

mainstream. Three randomized controlled trials (RCTs) have evaluated the efficacy and minimal adverse effects of propranolol for IH. The first RCT evaluated 40 patients who received either placebo or propranolol 2 mg/kg daily (divided into 3 doses) for 6 months; IH growth stopped by week 4 in the treatment group and the largest volume difference in IH was seen at week 12.[6] Léauté-Labrèze et al[7] demonstrated that propranolol could be given earlier to patients and at higher doses; the treatment group included 7 patients at 3 mg/kg daily of propranolol for 15 days, followed by 15 additional days of 4 mg/kg daily of propranolol. A statistically significant (P=.004) decrease in IH volume, quantified by use of ultrasonography, was exhibited by the propranolol group.[7] Lastly, the largest RCT (N=456) established the efficacy of propranolol 3 mg/kg daily for 6 months with a 60% successful treatment rate compared to 4% for patients receiving placebo.[8]

Given the efficacy of propranolol for IH, other investigators have experimented with nonselective beta-blockers for other dermatologic conditions. In addition to second-line use for flushing, hyperhidrosis, and adrenergic urticaria, the future of propranolol is expanding for vascular lesions in particular.[9] Chow et al[10] highlighted a case of progressive angiosarcoma of the scalp that responded to propranolol hydrochloride therapy at 40 mg 3 times daily with extensive regression; propranolol was given in addition to chemotherapy and radiation. The tumor was biopsied before and after propranolol therapy and exhibited a 34% decrease in the proliferative index (Ki-67).[10] Interestingly, Chisholm et al[11] evaluated the expression of β-adrenergic expression in 141 vascular lesions; endothelial cell expression of β_2-adrenergic receptors was found positive in 100% of IHs, 67% of kaposiform hemangioendotheliomas, 41% of angiosarcomas, 50% of pyogenic granulomas, and 75% of Kaposi sarcomas, to name merely a few studied lesions.

These data have spurred physicians to further seek beta-blocker dermatologic use in specific patient populations. For example, Meseguer-Yebra et al[12] employed timolol solution 0.5% twice daily for 12 weeks for 2 human immunodeficiency virus–negative patients with limited Kaposi sarcoma of the right thigh and foot; no clinical evidence of recurrence was seen at 20 months, and one of the patients had a subsequent biopsy performed with negative human herpesvirus 8 staining after therapy. In the pediatric arena, topical timolol has been used for both port-wine stains and pyogenic granulomas.[13-15] Two lesions of pyogenic granulomas on the scalp of a child were treated with timolol ophthalmic solution 0.5% under occlusion for 4 weeks with resolution.[15] Propranolol also has been utilized as adjunctive therapy for aggressive pediatric vascular lesions such as kaposiform hemangioendothelioma with promising results and additionally reducing the duration of therapy needed with vincristine.[2]

In summary, propranolol and timolol have made an indelible impression on the field of pediatric dermatology and have demonstrated a burgeoning role in the dermatologic arena. The use of nonselective beta-blockers for the management of vascular lesions can serve as adjunctive or monotherapy for certain patient populations. The relatively low adverse risk profile of propranolol makes it a versatile tool to use both systemically and topically. Although the authors of the study assessing the β_2-adrenergic expression in vascular lesions admittedly stated that the positivity of the receptors does not necessarily correlate with therapeutic management, it is an interesting subject area with much potential in the future.[11] This review serves to illuminate the expanding role of beta-blockers in dermatology.

REFERENCES

1. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med*. 2008;358:2649-2651.
2. Hermans DJ, van Beynum IM, van der Vijver RJ, et al. Kaposiform hemangioendothelioma with Kasabach-Merritt syndrome: a new indication for propranolol treatment. *J Pediatr Hematol Oncol*. 2011;33:E171-E173.
3. Guo S, Ni N. Topical treatment for capillary hemangioma of the eyelid using beta-blocker solution. *Arch Ophthalmol*. 2010;128:255-256.
4. Püttgen K, Lucky A, Adams D, et al. Topical timolol maleate treatment of infantile hemangiomas. *Pediatrics*. 2016;138:3.
5. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics*. 2013;131:128-140.
6. Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas [published online July 25, 2011]. *Pediatrics*. 2011;128:E259-E266.
7. Léauté-Labrèze C, Dumas de la Roque E, Nacka F, et al. Doubleblind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants < 4 months of age. *Br J Dermatol*. 2013;169:181-183.
8. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med*. 2015;372:735-746.
9. Shelley WB, Shelley ED. Adrenergic urticaria: a new form of stress induced hives. *Lancet*. 1985;2:1031-1033.
10. Chow W, Amaya CN, Rains S, et al. Growth attenuation of cutaneous angiosarcoma with propranolol-mediated β-blockade. *JAMA Dermatol*. 2015;151:1226-1229.

11. Chisholm KM, Chang KW, Truong MT, et al. β-adrenergic receptor expression in vascular tumors. *Mod Pathol*. 2012;25:1446-1451.
12. Meseguer-Yebra C, Cardeñoso-Álvarez, ME, Bordel-Gómez MT, et al. Successful treatment of classic Kaposi sarcoma with topical timolol: report of two cases. *Br J Dermatol*. 2015;173:860-862.
13. Passeron T, Maza A, Fontas E, et al. Treatment of port wine stains and pulsed dye laser and topical timolol: a multicenter randomized controlled trial. *Br J Dermatol*. 2014;170:1350-1353.
14. Wine LL, Goff KL, Lam JM, et al. Treatment of pediatric pyogenic granulomas using β-adrenergic receptor antagonist. *Pediatr Dermatol*. 2014;31:203-207.
15. Knöpfel N, Escudero-Góngora Mdel M, Bauzà A, et al. Timolol for the treatment of pyogenic granuloma (PG) in children. *J Am Acad Dermatol*. 2016; 75:E105-E106.