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Can Topical Beta-Blockers Reduce the Size of Superficial Infantile Hemangiomas of the Head and Neck?

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BACKGROUND

The serendipitous discovery of propranolol as a medical therapy for infantile hemangioma in 2008 resulted in a significant change in the treatment paradigm for patients with hemangioma.¹ The use of systemic propranolol is now widely used, either alone or in conjunction with other medications or surgical treatments. Although generally well tolerated, propranolol is typically initiated with observed monitoring of vitals on either an inpatient or outpatient manner due to the risk of adverse events. It is prescribed as a liquid formulation in three doses daily. The most common side effects include hypoglycemia and bradycardia. The use of a topical beta-blocker was initiated soon after systemic treatment was discovered, with the intention of reducing systemic side effects. An ophthalmic formulation of timolol for elevated intraocular pressure was already available. The formulations are timolol maleate 0.1% and timolol 0.5% gel-forming solution. Ocular administration of timolol maleate 0.1% results in high levels of systemic absorption and can cause bradycardia, but this is reduced significantly with use of the 0.5% gel-forming solution. Absorption is likely even less so when applied to the dermis instead of the eye. A formulation of 1% topical propranolol ointment is also available; it is less studied, but reports indicate that it has similar results as topical timolol. The indications for topical therapy are not clearly defined, yet systemic therapy has consensus indications: patients with advanced hemangioma causing functional deficits such as those located adjacent to orbit or in airway, and for those causing significant cosmetic deformity or ulceration. The effectiveness and indications for topical beta-blocker therapy had not been thoroughly studied until recently.

LITERATURE REVIEW

The literature on topical beta-blockers consists of mostly retrospective studies with few randomized controlled trials and few meta-analyses. Although the publications are numerous, there are multiple limitations to the literature. The reports classify lesions into superficial and deep categories, but this is not standardized. Similarly, the rating scales proposed in the studies below are not consistent. The dosing was most commonly twice

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daily. In patients who have multiple hemangiomas covering a larger surface area, there may be more systemic absorption that is responsible for the overall improvement that is not controlled for within the studies. It is noted that the use of topical beta-blocker therapy is not currently approved for use by the US Food and Drug Administration.

In one of the first larger series, a retrospective multi-center study reviewed 73 patients treated with topical beta-blocker (timolol maleate 0.1% or 0.5% gel-forming solution).² The majority of the cohort had superficial hemangiomas, and >95% demonstrated an improvement as measured by visual analog scoring. There was one patient who did not respond and one who had a side effect of poor sleep, so the medication was discontinued.

A randomized controlled study reported 60 patients compared topical timolol directly with laser (pulsed dye and neodymium:yttrium-aluminum-garnet [Nd:YAG]) therapy in the treatment of superficial and mixed hemangiomas.³ Improvement was quantified through blinded expert raters of photographs and skin analysis camera. Hemangiomas with a deep component responded better to laser therapy. Superficial hemangiomas had an “excellent” response in 40% of patients treated with topical timolol, and an improvement of “mild” or more was noted in 90%. Other agents have been directly compared. In one study, half of the superficial hemangioma was treated with topical timolol and the other half with an immune modulator, topical imiquimod.⁴ Fifty-four patients were included, and efficacy rates as graded by blinded photographs were similar, both >80%, but favored timolol. Timolol was preferred overall and in subcategories of color regression, side effects, and caregiver preference.

Lastly, a meta-analysis evaluating the evidence for topical beta-blocker use was published in 2015.⁵ This included 17 studies, two of which were randomized controlled trials and nine were prospective. When combined, over 550 patients were included, and there was only one reported systemic adverse event of poor sleep. The rate of response to treatment was 80% for superficial hemangioma. Subanalyses concluded that there was no significant difference between topical propranolol and topical timolol. None of the studies had a control group that was not treated.

BEST PRACTICE

Topical beta-blocker therapy (timolol 0.5% gel-forming solution is preferred over timolol maleate 0.1% and topical propranolol) is a safe treatment in a select group of patients that meets the following criteria: hemangioma is 1) superficial and 2) nonulcerated. The reported success rate for significant visual reduction of hemangioma size is estimated at 80%. Laser therapy (pulsed dye and Nd:YAG) can be an alternative or adjunctive treatment for lesions that extend into deep subcutaneous tissue if the family prefers to avoid systemic treatment. Limitations in these studies include retrospective cohorts, a lack of control group, possible lesion natural history, and observer bias. For lesions located on mucosal surfaces and in periocular region, systemic treatment with clinical monitoring is favored due to unpredictable systemic absorption with topical therapy.

Treatment for advanced hemangiomas that involve the deep soft tissue, mucosal surfaces, or the airway require multimodality treatment (systemic propranolol, steroid use, or surgical treatment), and the adjunctive role for topical beta-blocker therapy is a topic for future study.

LEVEL OF EVIDENCE

The level of evidence is 2. Although randomized controlled trials are included in the analysis, it does not reach level 1 evidence because patients were not randomized to a placebo compared to the intervention; they often compared two different medical or procedural interventions.

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Fig. 1.

A superficial hemangioma of the nasal columella that was treated with topical beta-blocker and improved significantly. This may be an example of an ideal lesion that is superficial and flat. Laser therapy was not needed after topical beta-blocker therapy. (A) Patient at 5 months of age and (B) patient at 8 months of age. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]