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THERAPEUTIC UPDATE

Infantile Hemangiomas

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Infantile hemangiomas (IH) are among the most common vascular lesions of infancy. The incidence rate of infantile hemangiomas is approximately 4.5%, with virtually all IH presenting before the age of 3 months.[1] Various hypotheses have been proposed regarding their pathogenesis. These include placental embolization, somatic mutation of an endothelial type cell, stimulation of endothelial progenitor cells by hypoxia and mediation of growth by aberrant growth factors (ie, VEGF).[2] Risk factors include female sex, Caucasian race, prematurity, low birth weight, and multiple gestations. Maternal risk factors include advanced maternal age, placenta previa, and pre-eclampsia.[3]

The natural history of infantile hemangiomas has been well characterized, most typically with early proliferation followed by gradual involution. Not all IH require treatment as most resolve without significant sequelae, but a significant minority require active intervention. Indications for treatment include ulceration, potential for permanent disfigurement and functional compromise. The challenge in treating IH is to identify which are likely to cause long-term complications or sequelae and to intervene before permanent damage has been done. An approach to risk stratification can help in decision making regarding which IH can be left to involute on their own and which require active treatment (Table 1).[4]

Management

The management of IH has been revolutionized by the serendipitous discovery by Léauté-Labrèze et al of the dramatic responses of infantile hemangiomas to beta blockers. The focus of our discussion of the various treatment options for IH emphasizes the approach to management in the "post-propranolol era" beginning in 2008 when this treatment option became available. A key management of therapy is *timing*. Many hemangiomas have reached their maximum growth very early, by 5 to 7 weeks of age. Most have completed or nearly completed growth by 3 months of age. For those that need treatment, "the sooner the better" to prevent complications or permanent scarring. Using knowledge of growth characteristics, the optimal time for referral for consideration of treatment is 4 weeks of age[5]!

Topical and Local Therapies

Topical and local therapies are an appropriate choice for small, localized and relatively superficial IH (eg, low to moderate-risk category). Timolol maleate, a topical beta blocker, is gaining popularity in the treatment of superficial hemangiomas. We typically use the gel forming solution (0.5%).[4] Timolol is FDA-approved for the treatment of glaucoma in infants. It is not approved for IH but there are hundreds of reports (in case series and case reports) of its use with largely favorable reports in pre-selected patients (where topical therapy might make a difference). It works more slowly than oral propranolol, with benefits often visible in a few weeks and continued improvement for several months. Theoretical side effects are similar to oral beta blockers, but have rarely been reported.[4] Treatment should be limited to 1 drop BID to TID in order to minimize the risk of systemic absorption, especially on mucosal or ulcerated surfaces.[6]

Intralesional triamcinolone (TAC) is helpful in the treatment of certain IH, particularly small to medium-sized facial IH (eg, lip

TABLE 1.

Risk Stratification and Reasons for Intervention		
Risk stratification	**Risk Feature**	**Reason for Intervention**
Very high risk	Segmental (>5 cm)- face or perineal area	Associated structural anomalies (PHACE or LUMBAR), ulceration, airway or visual compromise
High risk	Bulky lesion – face	Tissue distortion, risk of permanent scarring
	Early white discoloration	Marker for impending ulceration
	Central face	High risk of disfigurement
	Periorbital, perinasal, perioral	Possible functional compromise, high risk of disfigurement
Moderate risk	Lateral face, scalp, hands, feet	Disfigurement, possible functional compromise
	Body folds (ie perineum, axilla)	Risk of ulceration
	Segmental > 5 cm on trunk or extremities	Risk of ulceration and permanent residual skin changes
Low risk	Nonvisible areas of skin ie trunk and extremities	Low risk of disfigurement or functional compromise

Table adapted from Luu et al, 2013[4]

and nasal tip IH) which are a bit too deep for timolol, but are well-localized enough such that propranolol may not be (at least initially) indicated.[4] Triamcinolone acetonide at a concentration of 10 mg/ml can be injected every 3-4 weeks during the proliferative phase, taking care to evenly distribute the medication evenly throughout the target hemangioma. The dose should not exceed 1-2 mg/kg.[4] Side effects include bleeding, atrophy and possibly systemic absorption. Couto et al recently published a retrospective study looking at the efficacy and safety of intralesional TAC in 100 patients. None of the patients had systemic absorption and skin atrophy was observed in only 2% of participants[7].

Imiquimod 5% has been used in some centers as an alternative topical treatment. Qiu at al completed a retrospective study comparing timolol to imiquimod therapy. Although they had similar response rates and efficacy, there were more side effects recorded in the imiquimod group.[8] Cryotherapy has been used by some practitioners but has lost favor in recent years.

Systemic Therapies

In patients with identified high risk lesions, the goal is to begin systemic therapy before evidence of functional compromise or permanent disfigurement has developed. Lesions with aggressive growth, a high threat of functional impairment or sequelae and those not responding to local measures should be considered for systemic therapy.

Current first line systemic therapy is oral beta blockers for complicated infantile hemangiomas. Propranolol is the most commonly used formulation. It is a systemic non-selective beta blocker. A recent meta-analysis looked at 1264 patients enrolled in 41 studies. The response rate for propranolol was found to be 98%,[6] showing better efficacy and less toxicity than steroids.[4] The most common adverse events include sleep disturbance and cold extremities. Cardiovascular side effects (eg, hypotension or bradycardia) are surprisingly rare.[6] The risk of hypoglycemia can be decreased by feeding frequently, giving the medication after feeding, and avoiding long periods without eating (eg, prolonged periods of sleep) in infants <6 months of age.[4] In 2013, Martin et al published anticipatory guidance information that can be distributed to parents on propranolol initiation, outlining the side effects and monitoring required during therapy.[9]

> “In patients with identified high risk lesions, the goal is to begin systemic therapy before evidence of functional compromise or permanent disfigurement has developed.”

While a consensus statement published in 2013 helped to standardize the initiation of propranolol across treatment centers,[10] including the lack of need for hospitalization of older children and recommending a dose range of 1-3 mg/kg/d of propranolol divided TID, FDA approval of Hemangeol® has led to slightly different recommendation. This product is FDA-approved for infants aged 5 weeks of age (adjusted for gestational age) and older with BID dosing and lack of need for hospitalization for initiation of therapy unless other medical morbidities exist. For outpatient initiation, heart rate and blood pressure should be monitored before treatment and at 1h and 2h post treatment following the initial dose and in any dose increase over 0.5 mg/

kg/d. Patients less than 5 to 6 weeks of age or with medical comorbidities should be considered for a short inpatient stay for propranolol initiation. In the pivotal randomized controlled trial of Hemangeol®, 6 months of treatment was clearly superior to a duration of 3 months.[11] Some patients require even longer treatment courses of a year or more. Risk factors for rebound growth with tapering or stopping the medication include deep soft-tissue involvement and segmental distribution.[12]

Other beta blockers have also been reported to have beneficial effects, though in far smaller numbers. These include atenolol and nadolol. One reason they are being considered is because they do not cross the blood-brain barrier and could mitigate potential CNS effects on sleep and – although unproven – on development.[13] A proof of concept study by Pope et al reported greater improvement in patients treated with nadolol vs propranolol but conclusions are limited by the small size of the study.[14] Corticosteroids remain a therapeutic option when other treatments are contraindicated. However, they are no longer first-line therapy due to their relative lack of efficacy and more significant side effects when compared to propranolol.[15,16]

Laser and Surgical Therapy

For many years, pulse dye laser (PDL) has been used as either a mono- or adjuvant therapy. It has proven useful in reducing residual telangiectasia and redness in older children. Some providers consider it more useful early on, noting that early treatment with PDL with or without adjuvant systemic therapy may lead to a more rapid response and decrease the risk of more serious sequelae.[17] It may diminish pain and increase healing time in ulcerated lesions in the perineum.[2] Hemangiomas may ulcerate at lower fluences so it is important to start treatment at lower energy levels. The Nd-Yag laser has been used successfully to treat thicker, non-responsive lesions. Notably, there is a higher risk of scar with this laser.[2] Fractional CO_2 laser has been used to treat residual textural changes and scars. Ma et al reported successful treatment of deep hemangiomas with fractionated CO_2 laser used in combination with topical timolol.[18]

Excisional surgery is generally considered if there are residual skin changes after involution. However in certain cases earlier surgery is reasonable. Examples of this include for IH, which are very exophytic or pedunculated, where a scar is highly likely to be present even after involution or where medical therapies have failed to have expected effects. Emerging evidence suggests that most involution is completed by 3 to 4 years of age.[19] Hence it is always appropriate to re-evaluate around that age to consider what treatment options are needed if significant residua are still present.

Disclosure

Dr. Frieden is a consultant for Pierre Fabre Dermatology.

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