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Therapeutic reviews

Review of topical beta blockers as treatment for infantile hemangiomas

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ABSTRACT

The treatment of infantile hemangiomas changed from the use of oral corticosteroids to oral propranolol on the serendipitous discovery of propanolol's clinical effectiveness in 2008. Since then, clinicians have begun to use topical beta blockers—in particular, timolol maleate 0.5% gel forming solution—with good effect. Topical beta blockers are now used for lesions with both deep and superficial components and those that are amblyogenic. When initiated in the proliferative phase of the lesion, the effectiveness of the treatment can be seen within days. There is no consensus on dosing, treatment bioavailability, or clinical assessment of lesions, but these are topics for future research.

1. Introduction

Since Léauté-Labrèze and colleagues by chance discovered the usefulness of oral propranolol as an alternative to oral corticosteroids, the treatment of infantile hemangiomas has been radically altered.[23] Not only has the method of treatment changed, but as beta blockers have a reduced side effect profile compared with corticosteroids, the threshold for treatment has also changed.[24] Previously, lesions were treated if they caused functional problems by obstruction or compression. Ophthalmic lesions were treated only if they were potentially amblyogenic. Now, treatment is considered for cosmesis or to reduce permanent scarring.[24]

Infantile hemangiomas are common, particularly in female, white children of low birth weight, with approximately 6% affected.[42] They are often present at birth, although may not be noticed until a few weeks later when the lesion begins its proliferative phase. The lesions grow rapidly in the first few months of life before stabilizing and finally involuting. There are no reliable indicators to predict the degree and rate of involution.

During the proliferative phase, lesions may grow to cause distortion of adjacent structures. From an ophthalmic perspective, distortion of facial features, compression of the globe, or closure of lids, may all be amblyogenic through inducement of astigmatism, strabismus, or occlusion. Cases

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such as these have been highly successfully treated with oral propranolol.[11,23] Claerhout's review cites 2 series, and their own unpublished results, of treatment of periocular infantile hemangiomas with 2 mg/kg/day oral propranolol.[11] Characterizing success as stopping growth or reducing size, a 100% response can be achieved. They do note, however, that sudden stopping treatment may result in an increase in lesion size and therefore recommend weaning off medication.

Previous treatments have included oral or intralesional corticosteroids, pulsed dye laser, surgical excision, cyclophosphamide, vincristine, and interferon-alpha 2a. All these treatment modalities had significant side effect profiles.[29] The use of oral propranolol for infantile hemangiomas has become widespread since its introduction. In 2008, 7% of Blatt's patients with hemangiomas were treated with oral propranolol versus 46% treated with corticosteroids. In 2010, 54% were treated with beta blockers, with 9% receiving corticosteroids.[2] Concern has been expressed that the ubiquitous use of oral propranolol has occurred without any scrutiny or control.

A statement on the use of oral propranolol by members of a consensus conference held in 2011 was conservative because of the lack of high-quality clinical data.[12] They recommended that only children with lesions in the presence of ulceration, risk of permanent disfigurement, or impairment of vital function (visual or airway compromise) be treated. The statement recommended that these children have a normal cardiovascular and respiratory examination before treatment and that an echocardiogram should be performed on all who had heart rates outside the normal range and those with a personal or family history of congenital heart conditions or arrhythmia. Children with PHACE (Posterior fossa malformations, hemangiomas, Arterial anomalies, Cardiac defects, Eye abnormalities, sternal cleft and supraumbilical raphe) syndrome should have magnetic resonance imaging evaluation to assess the aortic arch and therefore estimate the risk of stroke while taking propranolol. The recommended dose of oral propranolol was 1–3 mg/kg/day, divided into 3 daily doses. On starting treatment, children less than or equal to 8 weeks gestational age should be admitted for monitoring, whereas all other children should be monitored with heart rates and blood pressures obtained at baseline and 1 and 2 hours after commencing treatment or after a dose increase. Kumar's survey of pediatric dermatologists found that, despite the consensus recommendations, 75% of clinicians used variations in dose, monitoring, history, and examination.[21]

Topical treatments were tried to avoid the potential side effects of oral beta blockers. Bonifazi first published the use of 1% propranolol ointment for 6 superficial hemangiomas in 2008, whereas Pope and Chakkittakaniyil began to use topical timolol maleate 0.5% gel in 2009.[3,36] A recent survey of pediatric dermatologists showed that 91% of those surveyed use topical timolol, 66% in conjunction with oral propranolol.[21] We review the use of topical beta blockers in the treatment of infantile hemangiomas.

2. Beta blockers method of action

The mechanism of action of beta blockers on hemangiomas is not completely understood. We know that vasoconstriction causes an immediate effect, but inhibition of angiogenesis and promotion of apoptosis has a more sustained response.[51,57]

Hadashick has shown that infantile hemangiomas have a high expression of beta 2-adrenoceptors through which propranolol exerts its mechanism of action.[15] Wong confirms both the presence of beta 1 and beta 2 adrenoceptors.[45] The vasoconstriction immediately impacts the flow of blood through the lesion, causing a change in the color from an intense purple-red to a lighter shade, associated with a palpable softening within a few days.

Infantile hemangiomas originate from mesenchymal cells, which differentiate to become hemogenic endothelial cells in the newborn. Propranolol *in vitro* affects hemogenic stem cells causing dysregulated adipogenesis and apoptosis. This may explain not only the early involution of lesions treated with propranolol but also its inability to completely remove the fatty residua of hemangiomas.[13] It is still not understood whether propranolol only targets actively proliferating hemangioma endothelial cells or whether the hemangioma endothelial cells have a unique response to propranolol.[51]

Propranolol reduces plasma renin activity, which in turn reduces angiotensin II levels. One hypothesis is that a local renin-angiotensin system is attenuated by topical beta blockers. Both angiotensin converting enzyme and angiotensin receptors have been found on the cell surfaces of immature capillaries within infantile hemangiomas.[17]

Plasma levels of renin are approximately 14 times higher at birth than in adulthood. Female, white, and premature children have even higher renin levels than other children, which may explain the propensity for these lesions in this population. High levels of renin in turn induce high levels of angiotensin II, which drives hemangioma proliferation and growth.[17]

In mouse models angiotensin II increases Pax-2 expression, which in turn activates Wnt. Wnt signaling is imperative in blocking apoptosis, preventing terminal adipocyte differentiation, and allowing accurate vascular endothelial growth factor–notch signaling. Vascular endothelial growth factor release by mesenchymal stem cells is necessary for endothelial progenitor cells to develop into endothelial cells. Angiotensin II stimulates production of osteoprotegerin, a glycoprotein found within proliferating infantile hemangiomas. Its role is to prevent tumor necrosis factor–related apoptosis ligand from interacting with functional death receptors, and thereby block apoptosis. Osteoprotegerin extends the lifespan of hemogenic endothelium, mesenchymal stem cells, and endothelial progenitor cells (Fig. 1). Angiotensin II therefore prevents apoptosis *via* the Wnt signaling pathway and the tumor necrosis factor pathway.[16]

Plasma renin levels naturally fall at the end of the first year in life, and the concurrent fall in angiotensin II leads to mesenchymal cell differentiation into adipocytes and fat deposition within hemangiomatous lesions. This mechanism explains the tendency for lesions to become fatty as they begin to involute at the age of 1 year.[16,17] Beta blockers expedite the fall in angiotensin II and enhance hemangioma involution.

Matrix metalloproteinase-9 has been linked to angiogenesis through modification of angiogenic growth factors such as vascular endothelial growth factor. Urinary matrix