Editorial

A β-antagonist for the treatment of infantile hemangiomas

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"Due to very high efficacy rates and fewer side effects than systemic corticosteroid therapy, β-blockers have become accepted as the first line in treatment of infantile hemangiomas."

Infantile hemangiomas are the most common vascular tumor of childhood, occurring in 5–10% of all infants up to 12 months of age [1]. β-antagonist therapy for the treatment of infantile hemangiomas has been a topic at the forefront of pediatric dermatology in recent years. Infantile hemangiomas are benign vascular tumors that may potentially impact development, cosmesis and overall comfort of the child. The efficacy of β-antagonist therapy, both topical and systemic, has been demonstrated [1,2]. Side effects, when compared with previous first-line systemic corticosteroids are much less frequent [1,3]. Serious complications from potential side effects of β-antagonist therapy can be avoided with careful dosing and good parental education.

β-antagonist mechanisms of action in the treatment of infantile hemangiomas are not fully known. The most commonly used systemic β-antagonist is propranolol. Propranolol is a nonselective β-adrenergic receptor blocker that is traditionally used for other indications, such as hypertension in both pediatric and adult patients, myocardial infarction, migraine prophylaxis and benign essential tremor. The general mechanism of action of propranolol is to block intrinsic catecholamines from binding G-protein-linked β1 or β2 receptors, preventing activation of the adenylate cyclase cascade [4,5]. There are few proposed mechanisms of action for how propranolol works in treating infantile hemangiomas. There is a possibility of early vasoconstriction and a reduction of blood flow, which can lead to the initial rapid improvement in color and softening [4]. Inhibition of VEGF, a growth factor that is critical to infantile hemangioma growth, is also a likely mechanism. In a study by Thaker *et al.*, an animal ovarian carcinoma model showed that catecholamines, which are blocked by propranolol, upregulated VEGF and increased angiogenesis [6]. Downregulation of other proangiogenic cytokines that are

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upregulated by catecholamines, such as the matrix metalloproteinases and IL-6, may also have a role in the overall effect propranolol has on infantile hemangiomas.

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Exact dosing of propranolol for the most optimized efficacy in the treatment of infantile hemangiomas has not been established. An oral dosing regimen of 0.5 mg/kg/day divided into two to three doses is recommended for the initial dose [1,5]. Starting with this dosage allows assessment of patient tolerability. Gradually increasing the dose to an oral dose of 2–3 mg/kg/day divided into three daily doses is currently recommended [5]. Prospective trials included intermittent heart rate and blood pressure monitoring for up to 3 h after the first dose [1,7]. Initial follow-up should be at 2 weeks with heart rate and blood pressure monitoring. If these parameters are within normal range for the child dependent on their age, then the dose can be increased to 2–3 mg/kg/day, divided into three doses. After this, monitoring of the heart rate and blood pressure can be carried out at 4 weeks after treatment initiation, and then monthly. Most dosing regimens are from small prospective trials and retrospective experience [1,7]. Before propranolol is started, some suggest cardiac workup including electrocardiography and in some cases echocardiography [7]. If PHACE syndrome is suspected, workup should also include MRI/magnetic resonance angiogram imaging of the head, as well as cardiology and neurology consultation [8]. Going forward, large prospective controlled trials are underway to further define use, dosing and safety of propranolol in treatment of infantile hemangiomas.

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Timolol maleate is also a nonselective β-adrenergic antagonist that is used topically to treat infantile hemangiomas with less systemic side effects than oral propranolol [9]. Different strengths have been used and all have shown to be efficacious in different studies [9–11]. Timolol comes as a gel with the most common strengths used being 0.1, 0.25 and 0.5%. Length of treatment ranged from 3 to 6 months, with extension of treatment usually 2 months further if the lesion seemed to enlarge after initial cessation of therapy [9,11].

Since 2008, when Léauté-Labrèze *et al.* reported an incidental finding of significant regression of a rapidly growing hemangioma in an infant who was placed on propranolol for cardiac indications, there have been a number of small studies on the efficacy of propranolol on infantile hemangiomas [12]. Most studies have been small and retrospective, but show positive results. A few small prospective trials have all shown very high efficacy rates. In four prospective studies, where the number of patients treated ranges from 15 to 55, efficacy rates range between 83 and 100% with respect to reduction in size of all hemangiomas, halting proliferation of rapidly proliferating hemangiomas and softening hemangiomas [1,7,13,14]. Topical application of timolol directly onto the hemangioma has also shown to be effective. Two prospective studies, one using 0.1% gel and the other using 0.5% gel demonstrated improvement in 100% of patients in terms of the appearance of the hemangioma and softening [9,15]. Greater improvement was seen in small and plaque-like hemangiomas over nodular type. Due to very high efficacy rates and fewer side effects than systemic corticosteroid therapy, β-blockers have become accepted as the first line in treatment of infantile hemangiomas.

Although side effects have been shown to be generally mild and rare with oral propranolol therapy, there is potential risk, and practitioners and parents alike need to be educated [1,7,8,13,14]. The most common side effects of propranolol are bradycardia and hypotension. Other commonly reported side effects include hypoglycemia, bronchial hyper-reactivity, congestive heart failure, sleep disturbance and digestive problems [16]. In most studies there were no reported side effects or the side effects were very mild requiring no child to be taken off the medication [13,16]. In another study, a child was taken off propranolol as a precautionary measure when the child developed unrelated bronchiolitis due to an infection, otherwise there were no other major side effects that warranted discontinuing propranolol use in this particular case series [7]. Peripheral vascular ischemic changes, such as skin mottling and extremity coldness, were cause to stop propranolol and resolved with no sequelae [14]. Hypoglycemia is a concern in all children on propranolol, but is especially of concern in infants younger than 2 months of age. Parents should be told to feed with the dosing of propranolol and to avoid prolonged periods of fasting. Parents should also be educated on the warning signs of hypoglycemia, which include both early (sweating, tachycardia, irritability and trembling) and late signs (lethargy, poor appetite and seizures) [8]. While the hypoglycemia is not caused by the

propanolol therapy, this β-blocker can mask all of the symptoms of low blood sugar except the sweating.

Larger prospective blinded trials are underway to guide dosing and further design the safety profile of propranolol and topical timolol gel. Currently, β-antagonist therapy seems to be a highly effective way of treating infantile hemangiomas with a low incidence of side effects.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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