

Propranolol in Infantile Hemangioma: A Review Article

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Hemangioma is the most common benign cutaneous vascular tumor in infants and children. The Hemangioma incidence in the neonates is 2% to 3% that increases to 10% in those younger than one year of age. Before introduction of propranolol in 2008, different medications such as systemic corticosteroids and vincristine, with different side effects, were used for years. Since then, over 200 studies concerning propranolol administration have been published. This study reviews propranolol use in infantile hemangioma.

Keywords: Propranolol; Infantile Hemangioma; Review Article

1. Introduction

Hemangioma is the most common benign cutaneous vascular tumor in infants and children, which is most commonly seen in head and neck region (1). These sorts of tumors generally present after the first or second week of birth. Typically, infantile hemangioma (IH) has a rapid proliferating phase, which lasts up to 12 months due to the abundance of α -smooth muscle actin (α -SMA)-positive perivascular cells, followed by an involuting phase that lasts one to five years, and a regressing period of five to ten years after the involuting phase (1-6). In the proliferative phase, vessels' endothelial cells are immature and disorganized. In involuting phase, however, the number of vessels is reduced and the vessels become mature and enlarged. Finally, connective tissue, fibroblasts, and fat cells replace the vascular tissue (2).

Complete regression of the lesions is observed in 50% and 90% of the five- and nine-year-old patients, respectively (7). A residual fibrofatty mass often persists after the involuting phase (8). In addition to the complications, IHs with deep and segmental components might have prolonged growth phase (9); some of these features include ulceration, disfigurement and scarring, impairment of function, and invasion to vital structures (10).

2. Epidemiology

The incidence of hemangioma in the neonates is 2% to 3% that increases to 10% in those under one year of age (1, 5). The prevalence raises to as high as 22% to 30% in preterm and low birth weight (< 1000 g) infants (1, 11). The prevalence of hemangioma is 10% to 12% in Caucasians, 1.4% in blacks, and 0.2% to 1.7% in Taiwanese and Japanese (10, 12). Hemangioma is more frequent among females

with male to female ratio ranging from 1:3 to 1:5 (1, 3). The etiology of hemangiomas remains unknown (1). Female, multiple gestation, gestational hypertension, and low birth weight are mentioned as important predisposing factors. Furthermore, fair skin and history of chorionic villus sampling might increase the risk of IHs (1, 10, 12).

A new hypothesis about IH states that trauma-induced hypoxia of fetus skin during pregnancy triggers neovascularization. Therefore, the prophylaxis from intrauterine and extrauterine trauma might prevent the formation of IHs (13).

3. Pathogenesis

The etiologic hypothesis suggests that different components including placenta-derived embolized cells (8), somatic mutations in endothelial cells in one or more genes that affect endothelial cell growth or progenitor cell, and clonal expansion of endothelial cells (8, 14) play important roles in pathogenesis of this disorder. It is noteworthy that hypoxia can stimulate inappropriate proliferation of the endothelial progenitor cells (8, 15).

Regulators of growth and involution of hemangioma are poorly understood. During the proliferative phase, proangiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) are abundant. VEGF-A is a main regulator of angiogenesis and vasculogenesis and its level increases during the proliferating phase in comparison to the involuting phase (2, 11, 16). Apoptosis occurs during the involution phase (11).

4. Clinical Presentation

Precursor lesions often present with telangiectasia, pal-

lor, bruise-like lesions, or rarely, ulceration at birth (8, 10). These lesions are most commonly seen in head and neck (60%) and trunk regions (25%). The extremities are the least common site (15%) (1, 7). Although most of hemangiomas have an uncomplicated clinical course and treatment is not necessary, approximately 10% of them require intervention because depending on their location, size, and speed of regression, they have a potential to cause painful ulcerations and hemorrhage as well as disfigurement and dysfunction, (14).

Lesions involving the periorbital and orbital area, central face, skin folds, anogenital area, sites at high risk for ulceration and severe hemorrhage, and multifocal hemangiomas require intervention and lesions causing respiratory obstruction, congestive heart failure, dysfunction, disfigurement, or hypothyroidism require urgent interventions (14, 16-18). Therapeutic intervention is usually needed even in uncomplicated hemangiomas to prevent any functional impairment, scarring, or disfigurement that might affect the patient's quality of life (19). Timely intervention is essential to decrease the risk of permanent scarring and poor outcome (20).

Various modalities including topical, systemic, and surgical approaches as well as laser therapy are used to treat IHs (20). Currently available medical therapies include systemic or intralesional steroids, bleomycin, vincristine, interferon alpha, and β -blockers. A substantial mechanism of drug-induced hemangioma regression is through the induction of apoptosis (5). Hemangioma cells express β_1 and β_2 adrenergic receptors; therefore, propranolol affects IHs through inhibition of β -adrenergic receptors (21).

5. Propranolol

Propranolol is a synthetic, nonselective, β -adrenergic receptor antagonist that lowers the heart rate (HR) and blood pressure (BP). Propranolol is highly lipophilic. Only 25% of orally administered propranolol reaches to the systemic circulation due to first-pass metabolism by the liver (14, 22, 23). The therapeutic effect of propranolol in hemangiomas was explained by Léauté-Labrèze et al. for the first time (24). Nowadays, propranolol is administered as the first-line treatment for hemangiomas (25). In March 2014, the United States Food and Drug Administration (FDA) approved Hemangeol (propranolol hydrochloride) as the first and only approved treatment for proliferating IH that requires systemic therapy (19). The advantages of propranolol include its rapid onset of action and good tolerability regardless of sex, age at beginning treatment, type of involvement, ulceration, or depth (19). Before introduction of propranolol in 2008, different medications such as systemic corticosteroids and vincristine, with different side effects, were used for years and since then, over 200 studies concerning propranolol administration have been published (26). Pro-

pranolol has been tried to treat different variants of IH at different locations. It is preferable to administer propranolol as early as possible, ie, before six months of age (26). Some hospitals admit the patients for the first few days under strict condition of monitoring the vital signs, regular feeding, and blood sugar measurement. On the other hand, others initiate therapy in an outpatient setting after being sure of normal preliminary measures such as electrocardiography, blood pressure, and blood glucose level (26). A meta-analysis study indicated that propranolol leads to a better response the treatment of IHs in comparison with corticosteroids (99% and < 90%, respectively) (5).

6. Mechanism of Action

Propranolol therapeutic effects are exerted through three mechanisms: (a) vasoconstriction via inhibiting release of nitric oxide (14, 27); (b) reduced expression of vascular VEGF, bFGF genes, and metalloproteinase matrix (MMP2/9); and (c) triggering apoptosis of capillary endothelial cells (4, 14, 24). Propranolol affects IHs-derived endothelial and stem cells and causes apoptosis in endothelial cells of hemangioma; however, it has no effect on hemangioma stem cells (HemSCs) (21). Generally, there are three main apoptotic pathways: the extrinsic or death-receptor pathway, the intrinsic or mitochondrial pathway, and the perforin/granzyme pathway (28). It has been reported that propranolol can induce apoptosis in IH endothelial cells via stimulating both intrinsic and extrinsic apoptotic pathways, which are important therapeutic mechanisms. Additionally, these proapoptotic effects were dose dependent (5). Propranolol has three different pharmacological targets. Early effects may lead to vasoconstriction due to decreased release of nitric oxide (14). This effect induces color reduction of the IHs from intense red to purple as well as softening the lesion within 24 to 72 hours of treatment (13). Intermediate effects are caused by the blockage of proangiogenic signals (VEGF, bFGF, and MMP2/9), which result in growth arrest (14) as well as persistent improvement in color and thickness of IHs (13). In addition, induction of apoptosis in proliferating endothelial cells and the resulted tumor regression are long-term effects of propranolol (13, 14). After six months of treatment, IHs lesions become nearly flat, and only persist in some cases with residual skin telangiectasia (13). Propranolol-resistant IHs are rare and usually observed during early childhood and during the proliferation phase (29). After withdrawing the administration of propranolol, the first observed phenomenon is a rapid re-coloration of the IH, which is explained by the arrest of pharmacologic vasoconstriction. This observation is common and does not require re-administration of propranolol. Based on our clinical experience, superficial telangiectasia can disappear spontaneously and if persists, it can be treated by pulsed dye laser (PDL) (13).

7. Topical Propranolol

Topical 1% propranolol ointment can be effective in treating superficial cutaneous hemangiomas. The treatment was well tolerated without significant side effects even in patients with numerous or large lesions (19). Bonifazi et al. (30) reported treatment of six cases with topical 1% propranolol oil-based cream. Karin Kunzi-Rapp has also tested the efficacy of topical application of propranolol ointment on 45 patients with IH (19). Some reports showed that combination therapy with topical and oral propranolol in addition to flash lamp PDL might be superior to any of these methods alone in treatment of IH in high-risk regions (19, 20).

8. Propranolol in Rare and Complicated Forms of Infantile Hemangiomas

There are some reports of “beard hemangioma” and Cyrano’s hemangioma that were successfully treated with oral propranolol. According to these reports, propranolol was effective in treatment of IHs in both genders and in ulcerating, segmental, and nonsegmental IHs. Moreover, they recommended discontinuing the treatment during episodes of bronchiolitis (4).

Although uncommon, PHACES syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac abnormalities, eye abnormalities, and sternal defects or supraumbilical raphe) might be underdiagnosed. Physicians should be aware of this syndrome and consider appropriate investigations to detect any associated anomalies before complications arise. Caution must be taken while initiating propranolol in patients with PHACES syndrome because of the increased risk of acute ischemic stroke due to probable presence of aplasia, hypoplasia, or occlusion of a major cerebral artery, especially when more than one vessel is involved or there is coarctation of the aorta. An investigation on patients with PHACES syndrome treated with propranolol revealed that in a group of 32 infants, neurologic status changed in only one patient during propranolol treatment; this case showed mild right hemiparesis that remained improved and static as long as propranolol was continued (25).

9. Indication of Treatment

Although most of IHs have an uncomplicated clinical course, approximately 10% of them require treatment because of rapid growth in vital parts, developing local complications such as ulceration, large or segmental IHs, hemangioma in vital sites (eg, nose, eyelids, ear, and lips), cosmetic reasons, or functional risks (31, 32). Hemangiomas may be life threatening when they are present at the upper airways and liver, causing local complications such as hemorrhage, ulceration, and necrosis that lead to septicemia or disseminated intravascular coagulation (31).

Cardiovascular diseases like sick sinus syndrome, sec-

ond- or third-degree AV block, and asthma are the absolute contraindications for propranolol therapy (31-33). Hypersensitivity to propranolol in first-degree relatives, diabetes mellitus, chronic renal insufficiency, cerebrovascular anomalies, sinus bradycardia, hypotension, first-degree AV block, and/or bronchial hyperreactivity are the relative contraindications to propranolol therapy (31, 32).

10. Dose of Propranolol

Protocols for initiation and monitoring propranolol vary. Recently, consensus guidelines from a multidisciplinary expert panel have been published. These recommendations are prone to evolve over time since they are based on the expert judgment rather than rigorous controlled studies and additional data are rapidly produced. These guidelines propose a brief inpatient hospitalization (five days) during therapeutic induction in younger than two-month-old infants (31). Propranolol is initiated at a dose of 0.5 mg/kg/d in three divided dosages, and is gradually increased to the desired dose. Despite development of various protocols, propranolol is usually administered at 1 to 3 mg/kg/d with many practitioners favoring 2 mg/kg/d (10, 34); for ulcerated IHs, propranolol doses is 2 to 3 mg/kg/d (35).

Heart rate and blood pressure should be monitored before treatment, at one and two hours of drug administration and after any increasing in dose beyond 0.5 mg/kg/d. Infants should be fed every four to six hours (10, 31). The risk of hypoglycemia is higher on the third and fifth days of therapy (31). A rebound growth has been reported following discontinuation of propranolol. Consequently, many physicians maintain treatment until the growth phase is completed, which can last up to one year of age in cases with deep or large IHs. Predisposing factors that might lead to rebound growth have not been recognized yet. Presently, the studies detecting these factors, which may help in determining the infants at risk for recurrence, are under way. Although the majority of investigations concern propranolol, the effect of other β -blockers such as atenolol, acebutolol, and nadolol in treatment of IHs have been studied (10).

Clinical alarm signs of hypotension, bradycardia, and hypoglycemia should be introduced to the parents. Frequent feeding, especially in the first two to three hours of propranolol administration can help to prevent hypoglycemia (23). Instead of abrupt discontinuation of propranolol, it should be tapered gradually over two weeks. Cardiac hypersensitivity may occur 24 to 48 hours after abrupt discontinuation of propranolol, peak at the fourth to eighth days of treatment, and diminish after two weeks (23).

11. Duration of Treatment

Treatment duration depends on the type of IH. In deep and mixed IHs, the duration of treatment is longer because the proliferation phase lasts longer; therefore,

treatment is continued until 12 to 16 months of age. In patients with ulceration, treatment is continued up to nine to 12 months of age due to the risk of ulceration recurrence. On the other hand, deep periorbital and airway IHs require long-term treatment of up to 15 to 18 months of age because of potentially life-threatening complications of swelling after cessation of treatment (36).

12. Monitoring the Patients

The factors that affect inpatient or outpatient care include patients' age, history of prematurity, hemangioma subtype, comorbidities, and the level of their parents' knowledge (23). Infants under three months of age need inpatient induction for closer monitoring because they are at higher risk for propranolol-induced hypoglycemia; however, home monitoring is possible for older infants (23). Before initiating propranolol therapy, checking baseline vital signs such as heart rate and blood pressure, finger-stick blood glucose, electrocardiography, and echocardiography are recommended.

13. Side Effects of Propranolol

The main potential adverse effects include bradycardia, hypotension, hypoglycemia, bronchospasm, constipation, congestive heart failure, nausea, vomiting, depression, abdominal cramping, sleep disturbance, and night terrors (8, 23, 31, 37). Other rarely reported side effects include gastroesophageal reflux, agitation, nightmares, sweats and cold hands, lethargy, seizure, restlessness, difficulty breathing, cold clammy skin, delayed capillary refill, and lack of appetite (8, 23, 38). Hypoglycemia is the most commonly noted side effect among patients with IHs who were treated with propranolol (39). Careful monitoring is required for small for gestational age and premature infants, those with failure to thrive, prolonged periods of fasting, or poor oral intake, eg, during an acute illness (8, 10). The warning signs of hypoglycemia are fussiness, poor feeding, apnea, loss of consciousness, seizures, and hypothermia. Therefore, propranolol should not be administered while decreasing the oral intake (37). Hyperkalemia has been reported after early initiation of propranolol therapy and might require treatment with furosemide (40).

14. Resistance to Propranolol

Ahogo et al. reported relapse risk of 12% in infants who were treated early with oral propranolol for six months. Segmental IHs and those with a deep component were mostly at risk of relapse. Females and those with lesions located on head and neck area had a higher risk of relapse. Nevertheless, the dosage of oral propranolol did not seem to have any influence on the risk of relapse (41).

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Authors' contributions

All authors had participated equally in this study.

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