

Review Article

Cardiovascular Drugs in Management of Infantile Hemangiomas

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Abstract

Infantile hemangiomas (IHs) are the most common benign vascular tumors in children. IHs are generally noticed within the first few days to months of life and are characterized by a rapid growth phase followed by an involution phase. Despite their benign and self-limited nature, some hemangiomas can be life-threatening, may cause complications such as ulceration and permanent disfigurement that requires the immediate treatment. Recently, propranolol, a nonselective β -blocker, has become a successful and safe treatment for IHs. The mechanism of action on IHs still remains unclear, although several mechanisms are suggested which includes vasoconstriction, inhibition of angiogenesis and inducement of apoptosis. More recently other cardiovascular drugs, such as nadolol, atenolol and captopril, have been explored for the same purpose. The reviewed literature implies that propranolol as well as selective β -blockers should be used as first-line therapy for treating IHs. Additional randomized controlled trails are necessary to explore long-term effects.

ABBREVIATIONS

IHs: Infantile Hemangiomas; PDL: Pulsed Dye Laser; cAMP: Cyclic Adenosine Monophosphate; PKA: Protein Kinase A; NO: Nitrogen Oxide; cGMP: Cyclic Guanosine Monophosphate; PKG: Protein Kinase G; VEGF: Vascular Endothelial Growth Factor; CNS: Central Nervous System; PRIHs: Propranolol-Resistant Infantile Hemangiomas; ACEi: Angiotensin Converting Enzyme Inhibitor

INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign vascular tumors of infancy with a frequency of approximately 3-10%. Female to male ratio is 3:1, prematurity and low birth weight (<1500 g) are considered to be potential predisposing factors [1,2]. IH appear within the first few weeks of life and their growth decelerates gradually during the first year of life (proliferative phase). A period of stabilization follows for few months, with spontaneous involution which lasts several years (involution phase) [3]. Most IH are asymptomatic and can be left untreated. However, IH of a particular concern, may result in airway obstruction, visual impairment, ulceration, bleeding and cosmetic disfigurement, may necessitate immediate treatment. There are no rigorous evidence-based studies to guide the therapy of IHs. Until 2008, systemic glucocorticoids had been the mainstay of therapy, associated with many potential side effects

[4]. Other therapies such as interferon- α and vincristine can be effective, but also carry the risk of potentially serious side effects [4]. Pulsed dye laser (PDL) [5] and surgery can be also helpful, but have a relatively limited role. PDL usually shows better results for the superficial hemangiomas and surgical excision of IHs is considered only rarely.

Since unexpected discovery of the beneficial effect of oral propranolol for IH in 2008 by Léauté-Labrèze et al. it radically changed the treatment strategies and had become the most popular therapy for IH [6-8]. Since then, propranolol efficacy in managing IHs has been repeatedly demonstrated [9]. In this review we summarize the published literature concerning the role of propranolol and other cardiovascular drugs in the treatment of IHs.

MECHANISM OF ACTION OF PROPRANOLOL

Propranolol is a highly lipophilic beta-adrenergic receptor blocker, which competitively inhibits β 1- and β 2-adrenoceptors with the same affinity. Propranolol is a pure antagonist without partial agonistic effects. Usually it is used for cardiovascular indications, but discovering its anti-proliferative effect on IH it has become more widely used.

After oral intake of propranolol it is almost completely and rapidly absorbed from gastrointestinal tract. Co-administration

with food appears to enhance bioavailability, which is comparatively low due to extensive first-pass metabolism in the liver. Only 20-25% of the dose reaches the systemic blood circulation [10] and the peak plasma level is achieved about 1-3 hours after ingestion. Propranolol is about 90% bound to plasma proteins. The duration of action of a single oral dose is longer than the half-life period (3 to 6 hours) and may be up to 12 hours. Metabolites of propranolol and very small amounts of unchanged drug are excreted in the urine.

The specific mechanism of action of propranolol on IHs still remains largely unknown. Previous studies have shown that angiogenesis and vasculogenesis are two main prevailing pathogenic mechanisms in the pathogenesis of IHs [11]. Imbalance in the process of vascular network construction may lead to tumor development and metastasis. Several mechanisms of action were hypothesized and include induction of vasoconstriction, inhibition of angiogenesis and stimulation of apoptosis. By interaction on β -adrenergic receptors propranolol inhibits the vasodilatation by blocking cAMP/PKA/NO/cGMP/PKG pathway and leads to vasoconstriction, reduces a blood flow within the hemangioma and induces lightening of the color and softening of the lesion [12]. Pan et al demonstrated the antiangiogenic properties of propranolol *in vitro* and that the propranolol was able to induce the regression of hemangioma cells via the inhibition of cell cycle progression, invasion, and tube formation, concomitantly with decreased NO and VEGF levels through the down-regulation [13]. Propranolol has also been reported to reduce the serum concentrations of other proangiogenic cytokines such as basic fibroblast growth factor and membrane-anchored proteinase- metalloproteinase-9 [14,15].

DOSAGE OF PROPRANOLOL AND DURATION OF TREATMENT

Commonly practiced administration of oral propranolol in infants is started with an initial dose of 0.5 mg/kg/day, and gradually is increased up to 2-3 mg/kg/day divided into 2-3 daily doses [16,17] after clearance of cardiopulmonary contraindications. Solman et al. suggested a treatment protocol for propranolol in IHs where authors advise starting with the lower dose of propranolol 0.5 mg/kg/day in three divided doses and very cautiously increase the dose up to 2 mg/kg/day with monthly weight-adjusted dose increments [18], unless IH respond well to the treatment. The treatment is usually stopped at 12-14 months of age, but occasionally longer treatment may be required because of recurrences [17]. Considering discontinuation of propranolol, gradual dose reduction is recommended.

A higher dose of 3mg/kg/day had been used in a large industry-sponsored randomized, double-blind controlled trial and demonstrated better efficacy compared to 1 mg/kg/day or placebo [19].

ADVERSE EFFECTS AND SAFETY

Adverse effects of propranolol are related to the β_1 and β_2 adrenergic receptors blocking, that induces the alterations associated to cardiovascular events, respiratory symptoms, gastrointestinal problems, central nervous system (CNS)

symptoms, metabolic and skin changes [20,21]. Most frequent adverse effects reported were sleep disturbances (3.7%) and asymptomatic or unspecified hypotension (2.8%), followed by somnolence (2.2%), cool or mottled extremities (1.7%), pulmonary symptoms including wheezing (1.4%), asymptomatic or unspecified bradycardia (0.9%), hypoglycemia (0.9%), gastroesophageal reflux or gastrointestinal upset (0.7%), symptomatic hypotension (0.3%), and symptomatic bradycardia (0.1%) [22].

Due to the high lipophilicity of propranolol it easily penetrates the blood-brain barrier and by blocking β adrenergic receptors it may cause various effects on CNS, which manifests in fatigue, insomnia, nightmares, night restlessness and sleep disturbance. Hurlemann et al. demonstrated that propranolol reduces human basolateral amygdala responses to fearful, neutral and happy facial expressions [23] by interruption locus ceruleus-noradrenaline connections in amygdala [24]. In the early stage of life these effects on CNS may not be apparent and the short follow-up periods may not allow sufficient time for propranolol-induced changes in CNS. This particular concern has led us to explore β -selective blockers in the treatment of IHs.

Impairment of growth during propranolol therapy has been occasionally reported, however after withdrawal of the medications it returns to normal [25]. Comparing children with IHs treated with propranolol to non treated healthy controls Moyakine et al. found no increased risk of growth impairment at age of 4 years in patients who were treated with propranolol for 6 months or longer [26].

A prospective study including 21 patients with various congenital heart defects treated with oral propranolol showed a good to excellent response on the treatment, with minimal adverse effects [27]. A retrospective study in 216 children with IHs treated with propranolol showed that the prevalence of respiratory episodes and recurrent respiratory episodes were similar to the control groups (8.3% vs 14%, $p=0.265$; 3.7% vs 6.5%, $p=0.274$, respectively), and that no wheezing episodes were detected within one week after propranolol initiation [Mei-Zahav et al. personal communication].

On the basis of existing reports the adverse effects mentioned above were mild and well-tolerated.

EFFICACY OF PROPRANOLOL

The remarkable efficacy of propranolol in proliferating IHs is well-established now [17,28-31]. The response rate of propranolol treatment is about 98% [32]. Grel et al. reported 100% response to the therapy with 35.7% very good response [33], Luo Y et al. reported 91,2% efficacy with 37,8% excellent response [29], Kupeli et al. reported 78% response with 57% very good response [31]. Not much is written about the efficacy of propranolol beyond the proliferation phase, although Vivas-Colmenares et al. and Zvulunov et al. reported therapeutical benefits even when treatment was initiated at an older age [34,35]. After stopping the treatment with propranolol the risk of recurrences seem to occur in approximately 20-40% of cases [29,36]. Giachetti et al. suggested long-term therapy to reduce the chance of relapses, as comparison the two groups in their study 12 months treatment showed much lower relapse rate

(5%), than 8 months treatment (90%) [37]. In 2011 Caussé et al. collected data from 14 centers about propranolol-resistant IHs (PRIHs) [38]. From the 1130 children treated with oral propranolol for IHs only 10 patients had no response to the therapy with ≥ 2 mg/kg/day for at least 4 weeks period of time. This supports the efficacy of the propranolol, although as PRIHs seems to be very rare phenomenon, further summery of these exceptional cases remains necessary. The major meta-analysis of 35 studies published in 2013 concluded that propranolol therapy of IHs bears high efficacy with rapid clinical improvement and low rate of severe complications [39].

OTHER BETA-BLOCKERS

Other β -blockers such as atenolol and nadolol may provide similar efficacy to propranolol in IHs treatment [40,41]. Abarzua-Araya et al. have presented the first cohort-blinded study comparing atenolol to propranolol for treatment of IH. Among all 23 patients thirteen was treated with atenolol and ten with propranolol. The results showed that atenolol had 53.8% of complete response and propranolol had 60% [40]. No significant differences were in presenting the adverse effects between both beta-blockers but atenolol has the advantage of the possible reduced number side effects connected to β_2 adrenergic receptors. Another cohort-blinded study comparing efficacy of nadolol to propranolol for IHs conducted in the Hospital for Sick Children demonstrated better response after 24 weeks of the treatment with nadolol ($97 \pm 3.0\%$) comparing to propranolol ($86 \pm 14.8\%$) [41]. More studies are needed to confirm these preliminary results.

It has been demonstrated that renin-angiotensin system components may play a role in the biology of IHs that leads to the option to use angiotensin converting enzyme inhibitor (ACEi) as a potential treatment. Tan et al. performed observational clinical trial on eight patients with problematic IHs [42]. Patients were treated with ACEi - captopril for 8-19 months. All patients were responding to the treatment, three patients showed dramatic response, two moderate responses and three slow responses. Contradictory results in a retrospective case study of 17 patients with IH who were treated with prednisolone and required treatment with ACEi captopril because of the drug-induced hypertension [43]. After 1-2 weeks treatment of prednisolone plus captopril only four patients demonstrated mild improvement, three showed no change and three were worse. After discontinuation of prednisolone, captopril administration continued for three weeks while further improvement was significantly low and seven patients showed worse response. From this small retrospective case series it appears that captopril alone was not enough to sustain the improvement in the IHs. Recently published randomized controlled trial by Zaher et al. also supports the efficacy of captopril for IHs, although comparing to propranolol, significantly better and faster response was noticed in the group of propranolol [44]. Also cardiac side effects were only reported in captopril-treated group. Captopril seems to be preferable for treating problematic IH in patients with relative contraindications to β -blockers, although more studies are needed.

CONCLUSION

In conclusion, increasing clinical evidences show the efficacy of β -blockers for treating IHs even at low doses and due to its few and well-tolerated adverse effects, propranolol appears to be an efficient and accessible way of treatment in children with IHs. We strongly recommend the use of propranolol as first-line medical treatment in all cases of complicated infantile hemangiomas.

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