**Name of journal: *World Journal of Cardiology***

**ESPS Manuscript NO: 20077**

**Manuscript type: MINIReviews**

**Cardiovascular drugs in the treatment of infantile hemangioma**

Fernandez-Pineda I *et al*. Cardiovascular drugs for infantile hemangioma

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**Author contributions:** Fernandez-Pineda I, Williams R, Ortega-Laureano L and Jones R designed the review article and wrote the manuscript.

**Conflict-of-interest statement:** Theauthors declare that there is no conflict of interests.

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**Telephone:** +1-901-5952315

**Received:** May 28, 2015

**Peer-review started:** June 1, 2015

**First decision:** August 16, 2015

**Revised:** September 4, 2015

**Accepted:** October 23, 2015

**Article in press:**

**Published online:**

**Abstract**

Since the introduction of propranolol in the treatment of complicated infantile hemangiomas (IH) in 2008, other different beta-blockers, including timolol, acetabutolol, nadolol and atenolol, have been successfully used for the same purpose. Various hypotheses including vasoconstriction, inhibition of angiogenesis and the induction of apoptosis in proliferating endothelial cells have been advanced as the potential beta-blocker-induced effect on the accelerated IH involution, although the exact mechanism of action of beta-blockers remains unknown. This has generated an extraordinary interest in IH research and has led to the discovery of the role of the renin-angiotensin system (RAS) in the biology of IH, providing a plausible explanation for the beta-blocker induced effect on IH involution and the development of new potential indications for RAS drugs such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in the treatment of IH. This review is focused on the current use of cardiovascular drugs in the treatment of IH.

**Key words:** infantile hemangioma; beta-blockers; renin-angiotensin system; angiogenesis

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**Core tip:** This article aimed to review the different beta-blockers used in the treatment of children with infantile hemangioma, the pre-treatment cardiologic work-up required and the potential side-effects associated with beta-blockers therapy in such a young population. Other cardiovascular drugs with potential effects on infantile hemangioma including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are also reviewed.

Fernandez-Pineda I, Williams R, Ortega-Laureano L, Jones R. Cardiovascular drugs in the treatment of infantile hemangioma. *World Journal of Cardiol* 2015; In press

**Introduction**

Infantile hemangiomas (IH) are not only the most common vascular tumors in children, but also the most common soft-tissue tumors in this population, occurring in 5% to 10% of infants[1,2]. Evolution of IH is characterized by a proliferation phase, stabilization, and a progressive spontaneous involution in the first 2-10 years of age[3]. Only 10%-15% of IHs results in complications requiring treatment[4]. Beta-blockers, especially propranolol, have emerged as first-line therapy and have dramatically changed the therapeutic approach for complicated IH, leaving systemic glucocorticoids as the second-line therapy. After the first publication in 2008[5] about the efficacy of propranolol in IH, more than 500 reports in the medical literature have supported its use as first-line therapy[6-10]. The largest, randomized, placebo controlled trial involving patients with complicated IHs treated for up to 24 wk with a pediatric oral propranolol solution has been recently published[6]. Other pharmacological agents including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) implicated in the renin-angiotensin system (RAS) have been tested for IH[11-13] (Table 1). This article aimed to review the current indications for beta-blockers in IH, the potential effects of RAS drugs in the treatment of IH and their role as antiangiogenic agents.

**Beta-blockers**

Beta adrenergic receptor blockers are a class of medications which exerts their action by blocking B1 and/or B2 adrenergic receptors that exist throughout the body. B1 are primarily represented in the myocardium and kidneys while B2 receptors are the predominant beta receptor in the extracardiac vasculature, skeletal muscle and lungs. Multiple forms of beta-blockers exist including B1 selective and nonselective beta-blockade. Beta-blockers cardiac function is by partially activating the beta receptors and thus not allowing norepinephrine or epinephrine to bind to the receptor. This causes a decreased amount of G stimulatory protein activation leading to decreased intracellular cyclic adenosine monophosphate (cAMP) which then decreases phosphorylation by protein kinase A. This in the myocardium leads to decreased heart rate and contractility. In the vasculature, B2 receptors are also coupled to G stimulatory proteins which when stimulated by norepinephrine or epinephrine lead to increased cAMP and intracellular calcium loading which yields smooth muscle relaxation. B2 antagonism therefore is associated with a small degree of vasoconstriction in many vascular beds. Beta-blockers have also been found to decrease vascular endothelial growth factor (VEGF) as well as bFGF through unknown mechanisms[13]. B antagonism has also been shown to decrease the renin formation in renal cells as cAMP signaling subsequent to B receptor activation is critical for basal expression of vessel associated renin[15].

**Angiotensin-converting enzyme inhibitors**

ACEIs function by preventing the angiotensin-converting enzyme (ACE) from cleaving angiotensin I (AT I) to create AT II. Normally, renin produced in the kidney as a result of sympathetic stimulation, hypotension or decreased sodium delivery to the nephrons cleaves the protein angiotensinogen to form AT I which is then converted by ACE to AT II. AT II then binds to AT I-receptors in smooth muscle and cause vasoconstriction. AT II also causes release of norepinephrine as well as preventing the reuptake of norepinephrine in sympathetic nerves. In addition, AT II causes an increase in the circulating aldosterone levels. By blocking these mechanisms, ACEIs therefore cause vasodilation of the vasculature with a resultant decrease in cardiac preload and afterload as well as decreasing the systemic blood pressure. ACEIs also down-regulate the sympathetic tone by preventing the release of norepinephrine in the sympathetic nerves. ACEIs additionally increase naturesis by helping to decrease aldosterone levels[11,12,16].

**Angiotensin-receptor blockers**

ARBs also work on the renin-angiotensin-aldosterone pathways but by a competitive antagonism of AT II binding to the AT I receptors. This results in the same decrease in vascular tone, sympathetic/norepinephrine release and aldosterone release. ARBs have also been shown to block transforming growth factor beta which is known to have angioproliferative properties[13,17].

**Beta-blockers and angiogenesis**

Since the serendipitous discovery of the use of propranolol in the treatment of complicated IHs in 2008[5], an interest in the role of beta-blockers in hypoxia-induced angiogenesis has been raised. Other conditions, including retinopathy of prematurity (ROP) and cancer, are also characterized by the presence of hypoxia-induced angiogenesis and a potential role for beta-blockers has been advocated[18]. Most IHs do not present a premonitory mark and they become apparent 1-3 wk after birth. A blanched area, a telangiectatic patch or a bruiselike lesion may be seen as a premonitory mark in the early neonatal period in some patients. A rapid growth of IH is normally seen in the first 3-4 mo after birth, followed by a slow growth or stable phase until the age of 1 year. Spontaneous involution occurs over the next several years[2,4]. However, the growth pattern differs from each patient and lesion. Deep IHs often appear later and continue to grow for a longer time than superficial IHs. The origin of IH remains unknown, but some authors support the hypothesis that IH may actually be a response to local tissue hypoxia, a homeostatic attempt to revascularize relatively hypoxic tissue with new blood vessels[19-23]. A well-known risk factor for IH is placental insufficiency and this might be the cause of prenatal hypoxia that triggers the angiogenesis process and the development of IH[24,25]. GLUT-1, a glucose transporter in the erythrocyte membrane, is recognized as a specific immunohistochemical marker for IH and an important sensor of hypoxia. GLUT-1 is present in IH during proliferation and involution phases and it has been recently demonstrated to be upregulated within hypoxic zones of mesenchymal tumors[26,27]. Another condition associated with hypoxia is the ROP, which is known to be related to an initial microvascular ischemic insult followed by abnormal hypoxia-induced neovascularization[28,29]. Both, IH and ROP, have a higher incidence and severity in neonates with lower gestational age and birth weight. Interestingly, both conditions occur in the early neonatal period and most of them resolve spontaneously without sequelae. VEGF is overexpressed in response to hypoxia and ischemia. Both, IH and ROP, have an overexpression of VEGF. Particularly in the retina, VEGF induces a pathological blood vessel formation at the junction between the vascularized retina and the avascular zone of the retina, also into the vitreous [30]. Anti-VEGF drugs, including bevacizumab and ranibizumab, have showed similar efficacy in the regression of ROP[31,32]. Kong *et al*[33] measured serum levels of bevacizumab and VEGF in premature infants with ROP and treated with intravitreal injection of bevacizumab and they concluded that clearance of bevacizumab from the bloodstream takes at least 2 mo in this age population. Because VEGF is crucial in the fetal organogenesis, concern about the anti-VEGF effect mediated by bevacizumab in premature infants exists. Beta-blockers have demonstrated to have a safer pharmacological profile in the pediatric population. Ristori *et al*[34] published the first demonstration that beta-blockers were protective against retinal angiogenesis in an animal model. Filippi *et al*[35] evaluated the safety and efficacy of oral propranolol administration in preterm newborns affected by an early phase of ROP and they concluded that propranolol counteracts the progression of ROP with a high incidence of adverse effects. The preterm infant with IH may not be the appropriate candidate for systemic propranolol use and instead a topical beta-blocker may be an alternative selection in this specific population. Topical ocular instillation of propranolol has shown to be safe in animal models and on-going studies will define its role in ROP[36]. For periocular IH, timolol, another beta-antagonist, has also been reported to be effective and may be a viable alternative to systemic propranolol therapy[37].

New anti-cancer agents are being developed in response to tumor chemoresistance and severe side effects of standard chemotherapeutic agents. Several drugs, including beta-blockers, ACEIs and ARBs, were originally approved for indications other than malignancies treatment, but recent investigations support their role as cytostatic agents[38]. Adrenergic activation may play a role in carcinogenesis and tumor progression by promoting production of VEGF. Expression of beta-adrenergic receptors has been demonstrated in several tumor types, including colon cancer, hepatocellular carcinoma, lung adenocarcinoma, prostate cancer and breast cancer[39]. Recent studies have suggested that angiotensin and beta-adrenergic blockade may modulate the development and progression of cancer. Engineer *et al*[40] evaluated 262 patients with colon cancer who were exposed to ACEIs, ARBs and beta-blockers and they concluded that exposure to a combination of beta-blockers and ACEIs/ARBs is associated with decreased tumor progression, decreased hospitalizations, and increased survival in patients with advanced colorectal cancer.

# Beta-blockers and infantile hemangioma

# The use of beta-blockers for the treatment of IH was serendipitously discovered when a patient with a large infantile hemangioma was treated for cardiomyopathy with propranolol which prompted a change in color, softening and decrease in size of the lesion in 2008[5]. The group from France then treated 10 other patients with propranolol resulting in similar decrease in size of the IH. There have been multiple retrospective, single-institution case series reporting the benefit of propranolol in treating IH. A meta-analysis from 2013 reviewed 1162 publications and included 41 studies in the analysis comparing corticosteroids and propranolol for the treatment of cutaneous IHs[41]. Sixteen reported the outcomes from corticosteroid use in 2629 patients and 25 examined propranolol use in 795 patients with a pooled response rate of 69% for corticosteroids and 97% for propranolol (*p* = 0.001).

There have been three randomized controlled trials addressing propranolol use in a few different manners. The first was a small study, which randomized 40 patients to propranolol at 2 mg/kg (divided three times daily) or placebo for 6 mo[42]. Propranolol halted growth after 4 wk of use and decreased volume, color and elevation when compared to placebo. Major side effects such as hypoglycemia, hypotension and bradycardia were not reported. The next randomized trial evaluated the difference between treatment with corticosteroids and propranolol in 19 patients at 3 vascular anomalies centers [43]. Treatment occurred until toxicities developed or clinical response was achieved. The corticosteroid group had quicker decrease in size of the lesion but also had more frequent severe adverse events limiting the length of treatment. No difference in response rate to the medications of the IH was found after 4 mo of treatment though all 11 patients had discontinued the steroids due to toxicity. A third randomized trial explored the possible additive effect corticosteroids and propranolol[44]. Thirty patients were randomized to one of three groups: propranolol (2-3 mg/kg/d), prednisolone (1-4 mg/kg/d) or combination therapy all for 3 mo. The group treated with propranolol had superior results to the prednisolone group and similar results to the combination therapy. Again, most patients treated with prednisolone stopped taking the drug early due to adverse events. The largest and most recent randomized trial examined the effect of propranolol at different doses and lengths of treatment[6]. In 456 patients, the optimal dosing was identified at 3 mg/kg/d for 6 mo with a response rate of 60% *vs* 4% for placebo. Response was defined as complete or near complete resolution of the lesion at 24 wk of treatment. After 5 wk of treatment, 88% of patients in the higher propranolol dosing group had a response to the medication. The known adverse events of hypoglycemia, hypotension, bradycardia and bronchospasm were infrequent and equivalent in both groups.

Other beta-blockers, including timolol, acetabutolol, nadolol and atenolol, have been successfully used in the treatment of IH. Topical treatment with timolol maleate gel has also been well studied with a randomized controlled trial published in 2013 [45]. Forty patients with superficial hemangiomas without ulceration or mucosal involvement were randomized to topical timolol gel 0.5% (twice daily) *vs* placebo. The treated group had smaller than expected lesions and improved color at 24 wk of treatment though minimal differences were identified at earlier time points. No adverse events were discerned in the treatment group.

Since propranolol is a lipophilic nonselective beta-blocker that crosses the blood-brain barrier, sleep disturbances have been associated with its use, being less frequent with hydrophilic drugs such as atenolol and nadolol. Some investigators have highlighted the importance of the beta-adrenergic system in memory modulation and the potential long-term memory loss of children with prolonged propranolol use. A pilot, cohort study by Pope *et al*[46] compared 10 patients in the nadolol group *vs* 9 historic controls in the propranolol group, matched on age and sex. The nadolol group had a superior response at 4, 12 and 24 wk assessments, decreasing sleep disturbances and potential concerns about long-term memory loss. The difference in response may be related to the longer half-life of nadolol, which may increase compliance and steady state effect of the drug. Blanchet *et al*[47] reported good results in 3 cases of subglottic hemangioma treated with acebutolol, a cardioselective beta-blocker. Acebutolol should theoretically have less adverse effects than propranolol due to it cardioselectivity, but more studies are necessary to compare the efficacy of this agent. Atenolol is a selective, cardiac beta-blockers and may decrease possible respiratory side effects. A small study, which randomized 23 patients to treatment with atenolol or propranolol revealed equivalent response rates, 54% *vs* 60% [48]. Prospective clinical trials are required to better define the role of each beta-antagonist and the agent selection according to the patient characteristics and the type of lesion.

Cardiology evaluation prior to starting propranolol has been routinely performed; however, there is no uniform evaluation. Most centers utilize an electrocardiogram and echocardiography in infants prior to starting treatment. Although are few limitations to starting therapy with propranolol based on abnormalities found on these studies, there can be other cardiac related issues found prior to starting which may require additional treatments. One study showed 21% of patients with IH had an additional cardiac abnormality found on echocardiography[49]. Another study has shown that pretreatment electrocardiogram is of limited value for patients with an unremarkable cardiovascular history and a normal heart rate and blood pressure[50]. The duration of treatment also can vary based off of multiple factors (Figure 1). Not all infantile hemangiomas will respond to beta-blocker therapy and may not require long term treatment. Most, however, recommend at least 3 mo prior to determining that there is no effect from the beta-blocker. The long term therapy in those who respond should be at a minimum of 6 mo. If there is a significant decrease in size of the hemangioma but not complete resolution, this can be continued for 12 mo. Routine cardiac follow-up should be determined by growth that is expected to occur for that age. Infants increase their weight and thus need dose adjustments more frequently than toddler age children and therefore require more frequent evaluation. These follow-up evaluations however should consist of monitoring for symptoms secondary to the beta-blocker, dosage adjustment for weight gain, and determination of effect of treatment.

Side effects of beta-blockers include hypotension, bradycardia, hypoglycemia, seizure, nightmares, bronchoconstriction, diarrhea and somnolence[51]. The hypotension and bradycardia seen is often asymptomatic and typically associated with the first dose. Most symptomatic hypoglycemia is associated with concomitant illness or poor oral intake around the time of seizure. This is usually seen within the first few days of therapy but may occur at any time assuming the dietary intake changes. Nonselective beta-blockers are thought to prevent catecholamine induced glycogenolysis, gluconeogenesis and lipolysis which lead to hypoglycemia. Seizure is thought to be related to the hypoglycemia. Bronchoconstriction is related to the effects on the smooth muscle in the bronchi which beta agonist cause bronchorelaxation and therefore this mechanism is blocked with beta-blockers. Sleep disturbances can be very difficult to evaluate in this patient population.

**Angiotensin-converting enzyme inhibitors and infantile hemangioma**

After the demonstration of the RAS components in the endothelium of IH, a greater interest on the role of cardiovascular drugs in the management of proliferating IH has emerged. It has been proposed that modulation of products of the RAS such as AT I, ACE, or AT II could represent an alternative therapeutic target. Tan *et al*[10] published an open-labelled observational clinical trial using captopril, an ACEI, in the treatment of problematic proliferating IH in 8 patients. All the lesions responded to captopril at a dosage of 1.5/kg/d with a transient mild renal impairment occurred in one patient. Treatment was discontinued at the age of 14 mo, except for one patient. In contrast, Christou *et al*[11] reported the results of 17 patients with IH who were treated with oral corticosteroid therapy and developed hypertension requiring treatment with captopril. They concluded that captopril alone did not sustain the corticosteroid-induced involution. Further clinical trials are required to better define the role of these cardiovascular drugs.

**Angiotensin-receptor blockers and infantile hemangioma**

A recent study aimed to investigate the effect of the angiotensin peptides and their agonists and antagonists on cellular proliferation in proliferating IH in vitro samples. A significant increase in cellular proliferation in the AT I and AT II treated IH tissues compared with control samples was found, suggesting a potential role for ACEIs and ARBs in the proliferation phase of IH[12].

**Conclusion**

Although very few reports have been published on the role of the RAS and some cardiovascular drugs such as beta-blockers, ACEIs and ARBs in the management of IH, clinical evidence supports the use of propranolol as first-line agent for complicated lesions. More basic and clinical studies are needed to investigate the potential effectiveness of other cardiovascular drugs.

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**P-Reviewer:** Lee TS, Lin GM **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**



**Figure 1 Therapeutic algorithm for oral propranolol treatment in infantile hemangioma.** BP: blood pressure; ECG: electrocardiogram; HR: heart rate.

**Table 1** **List of publications on the role of beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers in infantile hemangioma**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Authors** | **Study type** | ***n*** | **Median age****(range)** | **CV drugs** | **Conclusions** |
| Léauté-Labrèze *et al*[6] | Prospective, clinical trial | 456 | 103.8 ± 31.0 d | Propranolol | Propranolol was effective at a dose of 3 mg/kg/d for 6 mo |
| Abarzua-Araya *et al*[47] | Randomized double-blind controlled trial | 23 | 5.2 ± 3.5 mo (2-14 mo) | Atenolol *vs* Propranolol | Atenolol appears to be as effective as propranolol. |
| Léauté-Labrèze *et al*[10] | Randomized double-blind controlled trial | 14 | 12.5 wk | Propranolol | Propranolol may be given very early in infants with IH, to stop IH growth and thus prevent disabling scarring. |
| Blanchet *et al*[47] | Case series | 4 | 2 mo (1.5-3 mo) | Acebutolol | Acebutolol seems to present advantages for use in treating subglottic hemangiomas |
| Bauman *et al*[43] | Randomized investigator-blind controlled trial | 19 | 2 wk-6 mo | Propranolol *vs* Prednisolona | Both medications show similar efficacy. Propranolol should be the first line of therapy for symptomatic IH unless contraindicated or unless future studies demonstrate severe adverse effects |
| Chan *et al*[45] | Randomized controlled trial | 41 | 2.5 mo (5-24 mo) | Timolol | Topical timolol maleate 0.5% gel with a maximum dose of 0.5 mg per day is a safe and effective option for small superficial IHs that have not ulcerated and are not on mucosal surfaces |
| Pope *et al*[46] | Cohort- blinded study | 19 | 4.5 mo (1-92 mo) | Nadolol *vs* Propranolol | Patients with proliferative IH, treated with oral nadolol for 6 mo, experienced almost complete involution of their tumor, which was significantly different from patients treated with propranolol |
| Tan *et al*[11] | Open-labelled observational trial | 8 | 12.9 wk (5-22 wk) | Captopril | The response of IH to an ACEI supports a critical role for the RAS proteins in IH |
| Cristou *et al*[12] | Retrospective case series | 17 | 7.5 mo (4.5-15 mo) | Captopril | The striking improvement observed with propranolol has not been replicated with captopril. ACEI is not involved in IH involution and the mechanism of action |
| Itinteang *et al*[13] | Basic research-*In vitro* | 6 | 6 mo (4-8 mo) | RamiprilLosartan | Findings suggest a key regulatory roleof AT I and AT II in promoting cellular proliferation in IH, and establish a role for ACEIs and ARBs in the proliferation of IH |

ACEI: angiotensin-converting enzyme inhibitors; ARBs: Angiotensin-receptor blockers; AT I: angiotensin I; IH: infantile hemangioma.