MINIREVIEWS

Cardiovascular drugs in the treatment of infantile hemangioma

Israel Fernandez-Pineda, Regan Williams, Lucia Ortega-Laureano, Ryan Jones

Israel Fernandez-Pineda, Lucia Ortega-Laureano, Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN 38105, United States

Regan Williams, Department of Pediatric Surgery, Le Bonheur Children's Hospital, Memphis, TN 38105, United States

Ryan Jones, Department of Pediatric Cardiology, Le Bonheur Children's Hospital, Memphis, TN 38105, United States

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

Correspondence to: Israel Fernandez-Pineda, MD, Department of Surgery, St. Jude Children's Research Hospital, 332 N Lauderdale, Memphis, TN 38105,
United States. israel.fernandez-pineda@stjude.org
Telephone: +1-901-5952315

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.

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 J Cardiol* 2016; 8(1): 74-80 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i1/74.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i1.74

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[14]. 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

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

Ref.	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 per day for 6 mo
Abarzua-Araya et al[48]	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)	Ramipril Losartan	Findings suggest a key regulatory role of 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.

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]. Glucose transporter, type 1 (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 pro-gression 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 per day), prednisolone (1-4 mg/kg per day) 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 per day 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
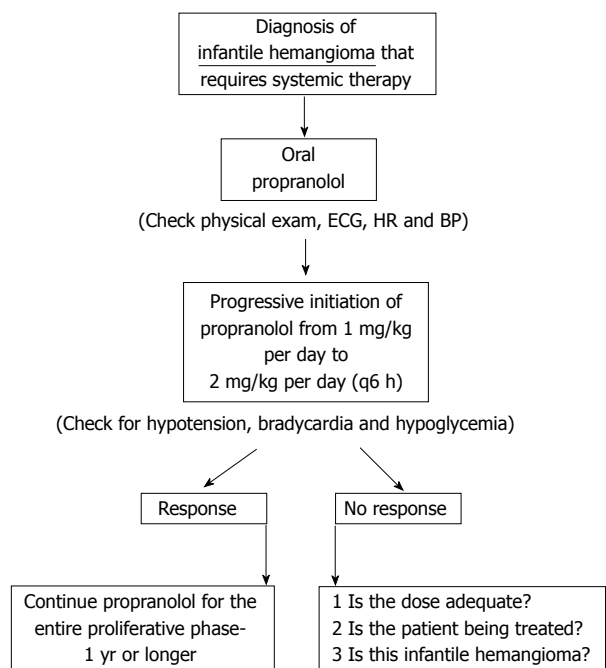
Figure 1 Therapeutic algorithm for oral propranolol treatment in infantile hemangioma. BP: Blood pressure; ECG: Electrocardiogram; HR: Heart rate.

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 electro-cardiogram 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 electro-cardiogram 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, bron-choconstriction, diarrhea and somnolence[51]. The hypotension and bradycardia seen is often asymp-tomatic 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 glyco-genolysis, 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*[11] 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 per day with a tran-sient 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*[12] 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.

REFERENCES

1   **Mulliken JB**, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**: 412-422 [PMID: 7063565 DOI: 10.1097/00006534-198203000-00002]

2   **Frieden IJ**, Eichenfield LF, Esterly NB, Geronemus R, Mallory SB. Guidelines of care for hemangiomas of infancy. American Academy of Dermatology Guidelines/Outcomes Committee. *J Am Acad Dermatol* 1997; **37**: 631-637 [PMID: 9344205 DOI: 10.1016/S0190-9622(97)70183-X]

3   **Enjolras O**, Mulliken JB. Vascular tumors and vascular malformations (new issues). *Adv Dermatol* 1997; **13**: 375-423 [PMID: 9551150]

4   **Kilcline C**, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol* 2008; **25**: 168-173 [PMID: 18429772 DOI: 10.1111/j.1525-1470.2008.00626.x]

5   **Léauté-Labrèze C**, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; **358**: 2649-2651 [PMID: 18550886 DOI: 10.1056/NEJMc0708819]

6   **Léauté-Labrèze C**, Hoeger P, Mazereeuw-Hautier J, Guibaud L, Baselga E, Posiunas G, Phillips RJ, Caceres H, Lopez Gutierrez JC, Ballona R, Friedlander SF, Powell J, Perek D, Metz B, Barbarot S, Maruani A, Szalai ZZ, Krol A, Boccara O, Foelster-Holst R, Febrer Bosch MI, Su J, Buckova H, Torrelo A, Cambazard F, Grantzow R, Wargon O, Wyrzykowski D, Roessler J, Bernabeu-Wittel J, Valencia AM, Przewratil P, Glick S, Pope E, Birchall N, Benjamin L, Mancini AJ, Vabres P, Souteyrand P, Frieden IJ, Berul CI, Mehta CR, Prey S, Boralevi F, Morgan CC, Heritier S, Delarue A, Voisard JJ. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med* 2015; **372**: 735-746 [PMID: 25693013 DOI: 10.1056/NEJMoa1404710]

7   **Sans V**, de la Roque ED, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J, Lipsker D, Dupuis E, Ezzedine K, Vergnes P, Taïeb A, Léauté-Labrèze C. Propranolol for severe infantile hemangiomas: follow-up report. *Pediatrics* 2009; **124**: e423-e431 [PMID: 19706583 DOI: 10.1542/peds.2008-3458]

8   **Price CJ**, Lattouf C, Baum B, McLeod M, Schachner LA, Duarte AM, Connelly EA. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. *Arch Dermatol* 2011; **147**: 1371-1376 [PMID: 21844428 DOI: 10.1001/archdermatol.2011.203]

9   **Bertrand J**, McCuaig C, Dubois J, Hatami A, Ondrejchak S, Powell J. Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study. *Pediatr Dermatol* 2011; **28**: 649-654 [PMID: 21995756 DOI: 10.1111/j.1525-1470.2011.01551.x]

10 **Léauté-Labrèze C**, Dumas de la Roque E, Nacka F, Abouelfath A, Grenier N, Rebola M, Ezzedine K, Moore N. Double-blind randomized pilot trial evaluating the efficacy of oral propranolol on infantile haemangiomas in infants & lt; 4 months of age. *Br J Dermatol* 2013; **169**: 181-183 [PMID: 23301692 DOI: 10.1111/bjd.12217]

11 **Tan ST**, Itinteang T, Day DJ, O'Donnell C, Mathy JA, Leadbitter P. Treatment of infantile haemangioma with captopril. *Br J Dermatol* 2012; **167**: 619-624 [PMID: 22533490 DOI: 10.1111/j.1365-2133.2012.11016.x]

12 **Christou EM**, Wargon O. Effect of captopril on infantile haemangiomas: a retrospective case series. *Australas J Dermatol* 2012; **53**: 216-218 [PMID: 22671578 DOI: 10.1111/j.1440-0960.2012.00901.x]

13 **Itinteang T**, Marsh R, Davis PF, Tan ST. Angiotensin II causes cellular proliferation in infantile haemangioma via angiotensin II receptor 2 activation. *J Clin Pathol* 2015; **68**: 346-350 [PMID: 25713419 DOI: 10.1136/jclinpath-2014-202794]

14 **Zhang L**, Mai HM, Zheng J, Zheng JW, Wang YA, Qin ZP, Li KL. Propranolol inhibits angiogenesis via down-regulating the expression of vascular endothelial growth factor in hemangioma derived stem cell. *Int J Clin Exp Pathol* 2014; **7**: 48-55 [PMID: 24427325]

15 **Neubauer B**, Machura K, Schnermann J, Wagner C. Renin expression in large renal vessels during fetal development depends on functional beta1/beta2-adrenergic receptors. *Am J Physiol Renal Physiol* 2011; **301**: F71-F77 [PMID: 21389089 DOI: 10.1152/ajprenal.00443.2010]

16 **Neal B**, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000; **356**: 1955-1964 [PMID: 11130523 DOI: 10.1016/S0140-6736(00)03307-9]

17 **Barreras A**, Gurk-Turner C. Angiotensin II receptor blockers. *Proc (Bayl Univ Med Cent)* 2003; **16**: 123-126 [PMID: 16278727]

18 **Filippi L**, Dal Monte M, Casini G, Daniotti M, Sereni F, Bagnoli P. Infantile hemangiomas, retinopathy of prematurity and cancer: a common pathogenetic role of the β-adrenergic system. *Med Res Rev* 2015; **35**: 619-652 [PMID: 25523517 DOI: 10.1002/med.21336]

19 **Drolet BA**, Frieden IJ. Characteristics of infantile hemangiomas as clues to pathogenesis: does hypoxia connect the dots? *Arch Dermatol* 2010; **146**: 1295-1299 [PMID: 21079070 DOI: 10.1001/archdermatol.2010.1295]

20 **Praveen V**, Vidavalur R, Rosenkrantz TS, Hussain N. Infantile hemangiomas and retinopathy of prematurity: possible association. *Pediatrics* 2009; **123**: e484-e489 [PMID: 19221153 DOI: 10.1542/peds.2007-0803]

21 **Hyland RM**, Komlósi K, Alleman BW, Tolnai M, Wood LM, Bell EF, Ertl T. Infantile hemangiomas and retinopathy of prematurity: clues to the regulation of vasculogenesis. *Eur J Pediatr* 2013; **172**: 803-809 [PMID: 23408311 DOI: 10.1007/s00431-013-1966-y]

22 **Itinteang T**, Withers AH, Davis PF, Tan ST. Biology of infantile hemangioma. *Front Surg* 2014; **1**: 38 [PMID: 25593962 DOI: 10.3389/fsurg.2014.00038]

23 **Ji Y**, Chen S, Xu C, Li L, Xiang B. The use of propranolol in the treatment of infantile haemangiomas: an update on potential mechanisms of action. *Br J Dermatol* 2015; **172**: 24-32 [PMID: 25196392 DOI: 10.1111/bjd.13388]

24 **North PE**, Waner M, Brodsky MC. Are infantile hemangioma of placental origin? *Ophthalmology* 2002; **109**: 223-224 [PMID: 11825799 DOI: 10.1016/S0161-6420(01)00994-0]

25 **López Gutiérrez JC**, Avila LF, Sosa G, Patron M. Placental anomalies in children with infantile hemangioma. *Pediatr Dermatol* 2007; **24**: 353-355 [PMID: 17845154 DOI: 10.1111/j.1525-1470.2007.00450.x]

26   **North PE**, Waner M, Mizeracki A, Mihm MC. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol* 2000; **31**: 11-22 [PMID: 10665907 DOI: 10.1016/S0046-8177(00)80192-6]

27   **Ahrens WA**, Ridenour RV, Caron BL, Miller DV, Folpe AL. GLUT-1 expression in mesenchymal tumors: an immunohisto-chemical study of 247 soft tissue and bone neoplasms. *Hum Pathol* 2008; **39**: 1519-1526 [PMID: 18620729 DOI: 10.1016/j.humpath.2008.03.002]

28   **Sapieha P**, Hamel D, Shao Z, Rivera JC, Zaniolo K, Joyal JS, Chemtob S. Proliferative retinopathies: angiogenesis that blinds. *Int J Biochem Cell Biol* 2010; **42**: 5-12 [PMID: 19836461 DOI: 10.1016/j.biocel.2009.10.006]

29   **Chen J**, Smith LE. Retinopathy of prematurity. *Angiogenesis* 2007; **10**: 133-140 [PMID: 17332988 DOI: 10.1007/s10456-007-9066-0]

30   **Penn JS**, Madan A, Caldwell RB, Bartoli M, Caldwell RW, Hartnett ME. Vascular endothelial growth factor in eye disease. *Prog Retin Eye Res* 2008; **27**: 331-371 [PMID: 18653375 DOI: 10.1016/j.preteyeres.2008.05.001]

31   **Hård AL**, Hellström A. On safety, pharmacokinetics and dosage of bevacizumab in ROP treatment - a review. *Acta Paediatr* 2011; **100**: 1523-1527 [PMID: 21854449 DOI: 10.1111/j.1651-2227.2011.02445.x]

32   **Darlow BA**, Ells AL, Gilbert CE, Gole GA, Quinn GE. Are we there yet? Bevacizumab therapy for retinopathy of prematurity. *Arch Dis Child Fetal Neonatal Ed* 2013; **98**: F170-F174 [PMID: 22209748 DOI: 10.1136/archdischild-2011-301148]

33   **Kong L**, Bhatt AR, Demny AB, Coats DK, Li A, Rahman EZ, Smith OE, Steinkuller PG. Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. *Invest Ophthalmol Vis Sci* 2015; **56**: 956-961 [PMID: 25613938 DOI: 10.1167/iovs.14-15842]

34   **Ristori C**, Filippi L, Dal Monte M, Martini D, Cammalleri M, Fortunato P, la Marca G, Fiorini P, Bagnoli P. Role of the adrenergic system in a mouse model of oxygen-induced retinopathy: antiangiogenic effects of beta-adrenoreceptor blockade. *Invest Ophthalmol Vis Sci* 2011; **52**: 155-170 [PMID: 20739470 DOI: 10.1167/iovs.10-5536]

35   **Filippi L**, Cavallaro G, Bagnoli P, Dal Monte M, Fiorini P, Donzelli G, Tinelli F, Araimo G, Cristofori G, la Marca G, Della Bona ML, La Torre A, Fortunato P, Furlanetto S, Osnaghi S, Mosca F. Oral propranolol for retinopathy of prematurity: risks, safety concerns, and perspectives. *J Pediatr* 2013; **163**: 1570-1577.e6 [PMID: 24054431 DOI: 10.1016/j.jpeds.2013.07.049]

36   **Liu H**, Yang MB, Li SK, Hao J. Effects of dosing protocol on distribution of propranolol in periocular tissues after topical ocular instillation. *Curr Eye Res* 2015; **40**: 638-645 [PMID: 25167079 DOI: 10.3109/02713683.2014.952830]

37   **Xue K**, Hildebrand GD. Deep periocular infantile capillary hemangiomas responding to topical application of timolol maleate, 0.5%, drops. *JAMA Ophthalmol* 2013; **131**: 1246-1248 [PMID: 23846584 DOI: 10.1001/jamaophthalmol.2013.4171]

38   **Rosenthal T**, Gavras I. Angiotensin inhibition and malignancies: a review. *J Hum Hypertens* 2009; **23**: 623-635 [PMID: 19339998 DOI: 10.1038/jhh.2009.21]

39   **Deshayes F**, Nahmias C. Angiotensin receptors: a new role in cancer? *Trends Endocrinol Metab* 2005; **16**: 293-299 [PMID: 16061390 DOI: 10.1016/j.tem.2005.07.009]

40   **Engineer DR**, Burney BO, Hayes TG, Garcia JM. Exposure to ACEI/ARB and β-Blockers Is Associated with Improved Survival and Decreased Tumor Progression and Hospitalizations in Patients with Advanced Colon Cancer. *Transl Oncol* 2013; **6**: 539-545 [PMID: 24151534 DOI: 10.1593/tlo.13346]

41   **Izadpanah A**, Izadpanah A, Kanevsky J, Belzile E, Schwarz K. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg* 2013; **131**: 601-613 [PMID: 23142941 DOI: 10.1097/PRS.0b013e31827c6fab]

42   **Hogeling M**, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. *Pediatrics* 2011; **128**: e259-e266 [PMID: 21788220 DOI: 10.1542/peds.2010-0029]

43   **Bauman NM**, McCarter RJ, Guzzetta PC, Shin JJ, Oh AK, Preciado DA, He J, Greene EA, Puttgen KB. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2014; **140**: 323-330 [PMID: 24526257 DOI: 10.1001/jamaoto.2013.6723]

44   **Malik MA**, Menon P, Rao KL, Samujh R. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: a randomized controlled study. *J Pediatr Surg* 2013; **48**: 2453-2459 [PMID: 24314186 DOI: 10.1016/j.jpedsurg.2013.08.020]

45   **Chan H**, McKay C, Adams S, Wargon O. RCT of timolol maleate gel for superficial infantile hemangiomas in 5- to 24-week-olds. *Pediatrics* 2013; **131**: e1739-e1747 [PMID: 23650294 DOI: 10.1542/peds.2012-3828]

46   **Pope E**, Chakkittakandiyil A, Lara-Corrales I, Maki E, Weinstein M. Expanding the therapeutic repertoire of infantile haemangiomas: cohort-blinded study of oral nadolol compared with propranolol. *Br J Dermatol* 2013; **168**: 222-224 [PMID: 22762503 DOI: 10.1111/j.1365-2133.2012.11131.x]

47   **Blanchet C**, Nicollas R, Bigorre M, Amedro P, Mondain M. Management of infantile subglottic hemangioma: acebutolol or propranolol? *Int J Pediatr Otorhinolaryngol* 2010; **74**: 959-961 [PMID: 20557953 DOI: 10.1016/j.ijporl.2010.05.013]

48   **Ábarzúa-Araya A**, Navarrete-Dechent CP, Heusser F, Retamal J, Zegpi-Trueba MS. Atenolol versus propranolol for the treatment of infantile hemangiomas: a randomized controlled study. *J Am Acad Dermatol* 2014; **70**: 1045-1049 [PMID: 24656727 DOI: 10.1016/j.jaad.2014.01.905]

49   **Blei F**, McElhinney DB, Guarini A, Presti S. Cardiac screening in infants with infantile hemangiomas before propranolol treatment. *Pediatr Dermatol* 2014; **31**: 465-470 [PMID: 24889812 DOI: 10.1111/pde.12344]

50   **Raphael MF**, Breugem CC, Vlasveld FA, de Graaf M, Slieker MG, Pasmans SG, Breur JM. Is cardiovascular evaluation necessary prior to and during beta-blocker therapy for infantile hemangiomas?: A cohort study. *J Am Acad Dermatol* 2015; **72**: 465-472 [PMID: 25592625 DOI: 10.1016/j.jaad.2014.12.019]

51   **Drolet BA**, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, Chun RH, Garzon MC, Holland KE, Liberman L, MacLellan-Tobert S, Mancini AJ, Metry D, Puttgen KB, Seefeldt M, Sidbury R, Ward KM, Blei F, Baselga E, Cassidy L, Darrow DH, Joachim S, Kwon EK, Martin K, Perkins J, Siegel DH, Boucek RJ, Frieden IJ. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics* 2013; **131**: 128-140 [PMID: 23266923 DOI: 10.1542/peds.2012-1691]

Baishideng®

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com