



## Update on Infantile Haemangioma

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### ABSTRACT

Infantile Haemangiomas (IH) are the most common vascular tumors occurring in early childhood, with a prevalence of approximately 5-10% of infants. These vascular tumors are divided into two main groups including; infantile haemangioma and vascular malformations. Although, haemangioma of infancy are common, benign and self-limited tumors, a significant percent of these lesions are associated with substantial morbidity in infancy and childhood.

All currently used treatments have significant risks. Dramatic improvement of complicated haemangioma of infancy to propranolol was recently reported.

Here in, we review infantile haemangioma as a whole with focus on the therapeutic efficacy of systemic and topical propranolol as a beta-blockers for the management of infantile haemangioma.

### Introduction

Infantile haemangioma (IH) is the most common vascular tumor that develops following proliferation of endothelial cells with different names such as Haemgioblastoma, capillary Haemangioma, Strawberry Navi, Hypertrophic Haemangioma, and Benign Haemangioendotheliomas.<sup>1,2</sup> IH occurs with an incidence of 5-10% in the infancy. About 1 in 20 children bear one type of haemangiomas. IH are more common among twins, Caucasians and

female infants. Female Infants are suffering from IH three to four folds more than male infants. Premature and low birth weight infants are more at risk of Haemangiomas. IH is developed in premature neonates 30% versus 5-10% of all infants.<sup>3-6</sup>

Proposed treatment modalities in medical textbooks and literature review are various. Propranolol, a well-known antihypertensive drug has been serendipitously noted to control

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the growth of haemangiomas. Beta-blockers are a class of drugs used for various indications, mainly for the management of cardiac arrhythmia, hypertension, migraines headaches and tremors. The therapeutic activity of beta-blockers is attributed to the blockade of  $\beta_1$ -adrenergic receptors ( $\beta_1$ -ARS) that are principally expressed in cardiac tissue.  $\beta_2$ -AR is expressed in the bronchial smooth muscle of the lung and other tissues and resembles  $\beta_1$ -AR in its molecular and pharmacological effects. The  $\beta$ -ARs a family of G-protein-coupled receptors that are activated by  $\beta$ -adrenergic agonists can initiate a series of signaling cascades, thus leading to multiple, cell specific responses.

$\beta$ -adrenergic signaling plays a role in basic developmental processes including the control of cell proliferation, differentiation and migration. According to this connection, emerging evidence suggests that  $\beta$ -blockers significantly reduce the proliferation either in vitro or in vivo, angiogenesis and metastasis of the most common human cancers, including adenocarcinoma of the breast, lung, pancreases, prostate, colon, stomach and IH.<sup>7</sup>

### Pathogenesis

Although the pathogenesis of haemangiomas is not clear, genetic factors have been suggested. Both angiogenesis and vasculogenesis have play a role in the pathogenesis of the IH.<sup>8</sup> IH is originated from endothelial stem cell and subsequently proliferate during vasculogenesis and migration of endothelial precursor cell to the area of new vessel formation following maturation of the cells.<sup>9</sup>

Haemangiomas develop during three phases: Proliferation, involution and involuted. The proliferative phase begins from shortly after birth and lasts to one year. It is usually shorter but seldom longer. During this phase, rapid proliferation of new blood vessels occurs arising in form of clonal primitive stem cells

and then differentiates into endothelial cells and pericytes. Involution initiates at the end of proliferative phase, usually around one year and continue for several years. Differentiation and apoptosis of endothelial cells is pursued by lobar deposition of fibrofatty tissue and the vessels remain more dilated in this phase. In the involuted phase, haemangioma converted to fibrofatty tissue and vessels are sparse.<sup>10</sup>

### Clinical manifestations and prognosis of the disease

Most of haemangiomas were not visible at birth and they become obvious as superficial and red color pallor skin lesions during the first days or within the first weeks of life. The lesions may involve each part of the skin, but the most common site of lesions are presented on head and neck 60%, trunk 25% and extremities 15% respectively.<sup>11</sup> Haemangiomas lesions are classified into three categories:

1. Superficial lesions can be identified as bright red nodule or papule that make white with pressure.
2. Deep lesions in which the color changes are dependent to the depth of the lesions that may be change to blue, purple or no color with pressure.
3. Combination of the two superficial and deep haemangiomas lesions

About 77% of haemangiomas are localized, 18% segmental and 5% multifocal.<sup>12, 13</sup>

Although each lesion has its specific growth pattern, most of them have six clinical stages including:

1. Nascent
2. Early proliferative
3. Late proliferative
4. Plateau
5. Involution
6. Abortive<sup>12, 14, 15</sup>

One of the obvious sign of haemangiomas is their rapid growth within early weeks of life in

infant that parents may become concerned about it. The most rapid growth of IH occurs on average at 5.5 to 7.5 weeks and 80% of haemangiomas obtain their maximum growth in five months of life.<sup>11</sup> Deeper haemangiomas tend to grow for longer time, while the superficial lesions involute earlier. Segmental haemangiomas grow more rapidly than focal type under 6 months. Eighty- five to 90% of IH are self-limited and have no side effects in most cases. Lesions which lead to remarkable deformity and malformation need earlier and faster treatment. These lesions are usually located on forehead, glabella, or central face >0.5cm in diameter, Nasal tip (Cyrano deformity), pinna, eyebrow and eyelid, any superficial thick haemangiomas of an area that is not easily covered by clothing, lip and perioral (may ulcerate and scar), and neck fold (may ulcerate and scar).<sup>10</sup>

Lesions with pain and threatening the function of vital organs or associated with more serious anomaly are also require to be treated. This classification can be helpful in decision making for the treatment of haemangioma before developing complications and serious sequel.<sup>10</sup>

Amblyopia is the most common ophthalmic side effect of IH in periorcular area that occur in 40-60% of IH Patients.<sup>16,17</sup> Most frequent complication of haemangiomas is ulceration that more commonly developed in ano-genital, lower lip and neck areas that may lead to significant blood loss, pain and tendency to secondary infection.

Other systematic complications associated with multifocal haemangiomas (more than five cutaneous lesions) are included: visceral involvement such as liver haemangioma, haemangiomas which lead to high- output heart failure and large segmental facial haemangiomas that is as a part of the PHACE syndrome (Posterior fossa malformations, Haemangioma, arterial abnormalities, cardiac defect/ aortic coarctiation and Eye

abnormalities). These lesions may resist to topical therapy and need multidisciplinary consultation and referring the patients to a related specialist.<sup>18</sup>

LUMBAR syndrome presents with segmental haemangiomas on the lower extremities and associated with these complications: lower extremities haemangiomas and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bone deformities, anorectal malformations, arterial anomalies and renal anomalies.<sup>19</sup>

Reticular haemangiomas defined as arrested growth haemangiomas on lower extremities are also associated with LUMBAR syndrome. Reticular haemangiomas typically in female infants are differentiated with ulcerative haemangiomas mainly localized on the lower extremities, buttocks or perineal area. The ulcerative lesions heal following scar formation.<sup>20</sup>

Infantile hepatic haemangiomas are histologically benign, clinically are usually silent and vascular proliferations occur in the setting of cutaneous hemangiomatosis. Although in most cases are asymptomatic, they may be recognized accidentally on prenatal or postnatal imaging studies. A few of hepatic haemangiomas are able to produce high output heart failure, hepatic failure, abdominal compartment syndrome or consumptive hypothyroidism secondary to production of type III iodothyronine deiodinase. These kinds of haemangiomas can be divided into three forms: focal, multifocal or diffuse. Multifocal are the most common form and often associated with multiple cutaneous IH.<sup>21</sup> However, most of hepatic haemangiomas have no need to be treated.

### Diagnosis

Most of the lesions are superficial and can be easily recognized clinically. There are several diagnostic methods for the lesions with unusual

appearance and abnormal growth pattern. Some of these diagnostic methods include: Magnetic Resonance Imaging (MRI), computer Tomography (CT), Sonography, angiography and measurement of serum Vascular Endothelial Growth Factor (VEGF) and urinary Basic Fibroblast Growth Factor (BFGF) markers of IH.

Biopsy from the lesions is necessary in cases of abnormal appearance or orbital lesions.<sup>22-25</sup>

### Differential diagnosis

There are various vascular tumors that mimic the appearance of IH. Vascular malformations have to be differentiated from IH. The lesions are non-proliferative and usually persist without regression which may enlarge with the patient's growth. The most common vascular malformation on head and neck is the capillary malformation that is also included: *navus flammeus* or port-wine stain. This lesion could be associated with *sturge-weber syndrome*. Their clinical appearance is similar to IH, but don't be light with pressure.

The other differential diagnoses include: *kaposiform haemangioendotheliomas* as rare invasive vascular tumor with rapid growth. *Tufted angiomas* are benign cutaneous and sub-cutaneous tumors with slow and progressive growth.<sup>8</sup> Both of these haemangiomas may be associated with *Kasabach- Merritt Syndrome*.<sup>26</sup>

### Management

Given that the prognosis of haemangiomas are usually benign and are resolved spontaneously, the patients can be followed-up without therapeutic intervention and parents should be alert that non-intervention can lead to achieve the best results.

Regular referring for measurement of the lesions and performing photography can be helpful to identify the prognosis of the disease

and especially the stage of healing of the lesions.

Full recovery gets in 50% of cases during 5 years and in 90% within 9 years of the first of life. Almost in 10% of cases, medical interventions are needed that included:<sup>4, 27</sup>

Rapid growth of facial haemangiomas with malformation, ano-genital haemangiomas, ophthalmic haemangiomas, oropharynx and larynx, ulceration of the lesions associated with secondary infection or not, *Kasabach- Meritte Syndrome*, diffused haemangiomas, heart failure and acute bleeding due to trauma.

Based on the guidelines of Care for Haemangiomas of Infancy published in the Journal of American academy of Dermatology, the main goals of management are as follows: prevention or reversal of life threatening side effects or functional- threaten complications, prevention of permanent malformations reducing of psychological stress for the patients and their family, avoidance of aggressive interventions in lesions with high-quality prognosis without treatment prevention or treatment of ulceration to reduce scarring, infection and pain.<sup>28</sup>

The medical interventions of IH depend on the size and location of the lesions, age of the patients, age of the lesion indicating the stage of IH and potential risk for sequelae of the lesions. All of these factors should be considered before final appropriate decision for treatment.<sup>8</sup>

Although, there is no gold standard treatment for IH, systemic steroid is the most common treatment that is associated with various toxicities in children such as failure to thrive, hypertension and hypertrophic obstructive cardiomyopathy. Current therapeutic implications include: Systemic steroid,<sup>29</sup> Intralesional steroids,<sup>30, 31</sup> Topical steroids,<sup>32</sup> Interferon- $\alpha$ ,<sup>33</sup> Vincristine,<sup>8</sup> cyclophosphamide,<sup>8</sup> Laser therapy,<sup>8, 30, 34</sup> and

Cryotherapy,<sup>35</sup> Surgery,<sup>36</sup> and Beta blockers.<sup>4,27,35-44</sup>

### A. Systemic steroid

Corticosteroids are the first line of treatment for life-threatening IH and functional- threaten of an organ. The aim of treatment with systematic corticosteroids was to prevent the growth of haemangiomas and decreasing their progression. So, the rapid phase of IH growth is the best time for treatment. The standard treatment is oral prednisolone given at a dose of 2-4 mg/kg up to 6 months, and 1-2 mg/kg of body weight (maximum of 60 mg) at monthly intervals. The dose depended on the age of the patient and size of the lesion. Clinical response can usually be observed within 2-4 weeks. After that, treatment should be continued with previous dose for 1 to 2 months and then gradually ceased within 4 to 6 weeks. Rapid termination of the treatment may lead to exacerbation of the lesions.<sup>29</sup>

In spite of the high therapeutic response rate, the following side effects are developed in 35% of cases: failure to thrive, cushingoid appearance, irritability and behavioral changes. A mixture of betamethasone 6mg/ml and triamcinolone 40 mg/ml in a 1:1 ratio is injected international, with a volume of 1-2 ml, depending on the size of the lesion. Local complications include risk of ophthalmic artery embolization, fat atrophy, calcification, cutaneous hypopigmentation and full thickness eyelid necrosis.

### B. Intralesional steroids

Intralesional injection of triamsinolone asetionide 3-5 mg/kg for 4-6 weeks into the lesions localized at vital area such as around the eyes can lead to the decrease of the lesions. Combination of triamsinolone and betametazone can be more effective.<sup>30, 31</sup>

### C. Topical steroids

Topical steroids with high therapeutic efficacy such as Clobetasol Propionate 0.05% once to twice per day or Halobetasol Propionate 0.05% and/or Betamethasone Di-Propionate are used for periocular lesions. Although topical steroids have no serious side effects of systemic steroids, they are associated with other complications such as atrophy, hypopigmentation, hypertrichosis, glaucoma and cataract.<sup>32</sup>

### D. Interferon- alpha

Life-threatening cases of IH that are unresponsiveness to systemic steroid therapy can be treated by subcutaneous interferon-alpha. Severe side effects of treatment with interferon- alpha are neutropenia and spastic diplegia.<sup>33</sup>

### E. Vincristine

Vincristine is an alkaloid agent that is used in chemotherapy and causes apoptosis of the cells. It is used as a steroid- sparing for the treatment of IH. The side effects of vincristine composed of: peripheral neuropathy, constipation, jaw pain and haematologic toxicity.<sup>8</sup>

### F. Laser therapy

Laser therapy is one of the non-medical modalities of treatment used in IH. Different kinds of laser including argon laser, Nd-YAG laser, CO2 laser, fractional photothermolysis and pulsed dye laser (PDL) were employed. Among these lasers, PDL with wavelength 585/nm was used for the treatment of superficial haemangiomas and telangectasia following the improvement of lesions successfully. Treatment is made up to 8 sessions or more every 1-2 months.<sup>8, 34</sup>

In a study by Hohenleutner et al., PDL arrested IH progression of 97% of cases, completely recovered 14% and partially regression occurred in 15%.<sup>30</sup>

It is proven that Nd-YAG laser is effective for deeper lesions with a significant scarring.

### G. Surgery

Surgery may be the best or the sole treatment in cases with risk of Kasabach- Merritt Syndrome or hepatic haemangiomas that had no response to medical treatment. Surgical approach may be selective for the treatment of localized haemangiomas of the upper eyelid or nose tip.<sup>36</sup>

### H. Beta blockers

In 2008, following the treatment of obstructive hypertrophic cardiomyopathy with oral propranolol 3mg/kg/day in a child with co-existing nasal infantile haemangiomas, there was a concurrent improvement of haemangiomas. Over the last few years, propranolol, as a non-selective  $\beta$ -blockers that has equal affinity for both  $\beta_1$  and  $\beta_2$  receptors by acting on multiple tissues has become increasingly a widespread successful during medication and choice with fewer side effects than other current treatment for IH.<sup>4</sup> Several other case reports and studies have been done with similar results.<sup>4, 27, 37- 46</sup>

Based on recent studies,  $\beta_2$  adrenergic receptors have been found in capillary endothelial cells of haemangiomas.<sup>47</sup> The mechanism of action of propranolol in the treatment of haemangiomas is thought to be by the three following different molecular mechanisms: vasoconstriction, inhibition of angiogenesis and induction of apoptosis.<sup>48</sup> Vasoconstriction leads to immediate changes in the IH due to decrease blood flow from the capillaries feeding the IH and can be observed as color, lightening and softening within the first three days of initiating of treatment. Epinephrine as an autonomic nervous system mediator plays a key role in the control of both vasoconstriction and vasodilatation by activating both the  $\beta_1$  receptors and  $\beta_2$  receptors.  $\beta$ -blockers like propranolol inhibit

epinephrine mediated vasodilatation and this leads to vasoconstriction of endothelial cells.<sup>49</sup> Angiogenesis is vital for tumor growth and progression.<sup>7</sup> Basic fibroblast factor and vascular endothelial growth factors (VEGF) are two major proangiogenic factors that increase during the growth phase of haemangiomas and current studies have shown VEGF is decreased by  $\beta$ -blockers like propranolol that leads to the inhibition of angiogenesis.<sup>50</sup> Cell proliferation control of tumors may be an effective treatment strategies. The Epinephrine and norepinephrine neurotransmitters can induce cell proliferation in different cancer types. These effects are mediated primarily via  $\beta_2$  adrenergic receptor activation in cyclic adenosine monophosphate– protein kinase (CAMP-PKA) signaling pathway in tumor cells. Propranolol can inhibit proliferation of tumors.<sup>51,52</sup>

Apoptosis is a type of cell death with features that are different from those of necrosis.<sup>53, 54</sup> It has been hypothesized that  $\beta_1$  adrenoceptor is one of the probable receptors involved in apoptosis and propranolol blocking the  $\beta_1$  adrenoceptor induces apoptosis at an increased rate.<sup>55</sup>

A precise history and physical examination to exclude reactive airway or cardiac disease and blood pressure are necessary to initiate of treatment with beta-blockers. Initial dosing of propranolol starts at 0.5 mg/kg/ per/day divided three times daily. Increasing the dose of propranolol to a maximum of 1-3 mg/kg/day for 3-12 months has been successfully used for the treatment of IH. Some clinicians continue the treatment up to beginning regression of the lesions or their complete repair.<sup>46</sup>

Several case reports and series including periocular cases have demonstrated positive results from moderate regression to 100% arrest of progression of the IH lesions.<sup>4, 56, 57</sup>

The probable complications of propranolol is composed of: somnolence, gastro- esophageal reflux, allergic reaction, respiratory syncytial virus (RSV), exacerbation, insomnia, agitation, nightmares, profused sweats, asthma onset, cold hands, hypotension, gastrointestinal upset, intermittent fatigue, spitting, shaking episodes following missing dose, hypoglycemia, diarrhea, sleep change and bradycardia.<sup>58</sup>

Hypoglycemia is the most serious reported side effect of propranolol following its use for infantile haemangiomas.<sup>59</sup> No significant cardiovascular morbidity has been revealed in a study performed on paediatric  $\beta$ -blocker toxicity.<sup>60</sup>

Topical beta-blockers have been also investigated in an effort to reduce the systemic side effects of oral propranolol. Topical Timolol Maleate ophthalmic drop is a non-selective beta adrenergic receptor antagonist that has been used for treatment of glaucoma in children and adults 30 years ago. Currently, topical Timolol has been reported in use for the treatment of cutaneous haemangiomas. The available formulation of Timolol in Us is ophthalmic Jel-forming solution 0.25% and 0.5%. Applying topical timolol 0.5% twice daily for treatment of IH causing significant astigmatism was associated with significant improvement in the size, thickness and color of the IH with any side effects.<sup>61, 62</sup>

In a retrospective study performed in five academic centers on 73 patients with haemangiomas, the results revealed that prolonged administration of Timolol 0.5% had been effective for treatment of superficial haemangiomas. The mean duration of treatment was 4.5 months and only one newborn had no response to the therapy.

The age of the patients did not have influence on therapeutic response and no rebound occurred after cessation of the treatment. Systemic complications following prolonged use of eye drops include apnea, asthma, mild

and transient headache, symptomatic bradycardia and the dermatologic side effects of Timolol include alopecia, psoriasis form rash, urticaria and contact allergy and angioedema.<sup>60-66</sup>

Intralesional injection of  $\beta$ -blockers has been performed by Awadein et al. in 2011 to evaluate the effectiveness of propranolol for the treatment of periocular capillary haemangiomas. In this prospective, uncontrolled non-randomized study, they compared the effect of intralesional triamcinolone 40mg/ml with intralesional propranolol 1mg/ml (up to 1 ml). In this study, they have found similar results with no side effects and suggested further investigation to explore the safety and efficacy of intralesional in addition to intravascular beta-blocker therapy.<sup>67</sup>

## Conclusions

There are clear evidences about therapeutic effects of propranolol in IH. Alternatively, systemic and local steroids, alpha-interferon, vincristine, cyclophosphomide, surgical excision and laser are the other therapeutic managements with their own side effects.

Propranolol is the first line of treatment of IH in many therapeutic centers because of its lower complications and response rate.

Other beta-blockers such as nadalol, acebutolol, atenolol, and topical timolol have been showed to be effective; however the majority of reports are related to propranolol.<sup>35</sup> The early, intermediate and long-term effects of propranolol on IH can be attributed to three different pharmacological targets. Early effects are attributable to vasoconstriction due to decreased release of nitric oxide. Intermediate effects are due to the blocking of proangiogenic signals (vascular endothelial growth factor, basic fibroblast growth factor, matrix metalloproteinase) and result in growth arrest.

Long-term effects of propranolol are characterized by the induction of apoptosis in proliferating endothelial cells, and the result in tumor regression. There are concerns about the use of propranolol as the main therapeutic agents. First it must only be used for complicated haemangiomas and not for the simple and safe haemangiomas and the probable side effects should be considered. On the other hand, further studies are needed about safety and the effectiveness of propranolol.

Although the published articles have shown no evidence that propranolol was as effective as the other steroid agents or more effective than the others on IH, propranolol has been used as the first line of IH treatment by many of dermatologists. Further studies are needed to compare the effect of steroid and propranolol on IH. The current available data indicated that propranolol could be the second line of treatment. Further studies may change the indications of using propranolol. Preparing a guideline about using and monitoring of propranolol seems to be necessary.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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