Evolving strategy in treatment of infantile hemangiomas: from steroids to propranolol

İnfantil hemanjiyomlarda steroidlerden propranolole gelişen tedavi stratejisi

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Abstract

Infantile hemangiomas are the most common vascular tumors of the early childhood. Increased incidence of infantile hemangiomas can be attributed to widespread use of assisted reproductive technologies. Majority of hemangiomas in infantile age group resolve spontaneously and only a small proportion of the cases with infantile hemangiomas requires treatment. GLUT-ONE acronym (Giant infantile hemangiomas, Liver and/or other visceral organ involvement, Ulcerated or bleeding infantile hemangiomas, Threatening of life, Organ dysfunctioning infantile hemangiomas, Non-localized infantile hemangiomas, Esthetic/cosmetic compromise) can help clinicians for the rapid decision of treatment. Corticosteroids have long been the mainstay treatment for hemangiomatous lesions but after the description of antiproliferative effect of propranolol on severe infantile hemangiomas in 2008, propranolol has been the preferred choice of treatment in many centers. Future studies should be directed to answer the questions regarding the optimal duration of propranolol treatment to overcome recurrences and clinical and histopathological characteristics of infantile hemangiomas that failed treatment with propranolol.

Key words: Infantile hemangiomas, steroids, propranolol, treatment indications, glut-one

INTRODUCTION

The impressive discovery of efficacy of propranolol in treatment of infantile hemangiomas (IH) represent an effective, inexpensive, readily available and safe therapeutic innovation for most of the cases with IH. In many centers propranolol has become the first line treatment option in treatment of IH\(^3\). Large-scale phase III clinical trials are needed to determine optimal dosing for propranolol and long-term safety profiles. Optimal duration of treatment and treatment failure in some cases with propranolol remain as two major problems to be resolved. Future studies should be directed to answer the questions regarding the optimal duration of propranolol treatment to overcome recurrences and clinical and histopathological characteristics of IH that failed treatment with propranolol. GLUT-
ONE acronym (Giant IH, Liver and/or other visceral organ involvement, Ulcerated or bleeding IH, Threatening of life, Organ dysfunctioning IH, Non-localized IH, Esthetic/cosmetic compromise) can assist clinicians to remember the indications for treatment as IH are GLUT-1 positive vascular tumors. The aim of this review is to describe the development in medical treatment of IH, to emphasize indications of treatment and to call the clinicians’ attention to revolutionary role of propranolol.

INFANTILE HEMANGIOMAS

Infantile hemangiomas (IH) are the most common vascular tumors of the early childhood with an incidence rate of 1.1%-2.6% among full-term neonates. These benign endothelial tumors can present in a large spectrum; from superficial hemangiomas to life threatening laryngeal hemangiomas or giant lesions in visceral organs. The place of IH among other vascular anomalies can be seen in Table 1. They are classified as glucose transporter-one (GLUT-1) positive vascular tumors. Widespread use of assisted reproductive technologies can be proposed to be responsible from increased incidence of IH.

Proposed risk factors for development of IH are summarized in Table 2. In infantile period, small percent of the lesions can cause organ dysfunction such as defects in vision, auditory disturbances, difficulty in feeding depending on the localization and esthetic-cosmetic compromise especially in head and neck region. Most of the patients with IH however, present with non-symptomatic superficial lesions.

Table 1. Classification of vascular tumors and malformations

<table>
<thead>
<tr>
<th>Vascular tumors</th>
<th>Vascular malformations</th>
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<tbody>
<tr>
<td>Infantile hemangiomas</td>
<td>Capillary malformation</td>
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<td>Congenital hemangiomas</td>
<td>Venous malformation</td>
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<tr>
<td>Tufted angioma</td>
<td>Lymphatic malformation</td>
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<tr>
<td>Kaposiform hemangioendotheloma</td>
<td>Arterial malformation</td>
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<td>Spindle cell hemangioendotheloma</td>
<td>Arteriovenous malformation</td>
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<td>Other, rare hemangioendotheloma</td>
<td>Combined malformations</td>
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<td>Dermatologic acquired vascular tumors</td>
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Morphologically, superficial, deep and mixed types can be differentiated. According to their distribution IH may either originate from a central focus as in the case of localized hemangiomas, or they can involve a broad anatomic region or significant portion of a developmental segment. The latter type of IH are named as segmental hemangiomas from embryological point of view. On the other hand, multifocal hemangiomas are composed of ≥5 non-contiguous lesions and frequently associated with lesions in visceral organs. Indeterminate type of IH show characteristics of at least two different types of hemangiomas.

Hemangiomas localized in head and neck region occasionally can be a component of PHACES syndrome, especially if accompanying abnormalities in posterior fossa, heart, aorta, eye and sternum exist. Suspected cases must be investigated by a multidisciplinary approach including examination by an ophthalmologist, radiologist, cardiologist and neurologist. Kasabach-Merritt syndrome, a consumptive cosgulopathy characterized by severe thrombocytopenia and hypofibrinoginemia can be encountered rarely in case of large hemangiomatous lesions. The mortality rate from hemorrhagic complications may be as high as 30%.

Table 2. Risk factors for infantile hemangiomas

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<th>Risk factors</th>
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<tr>
<td>Caucasian origin</td>
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<tr>
<td>Advanced maternal age</td>
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<tr>
<td>In-vitro fertilization</td>
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<td>Multiple pregnancies</td>
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<td>Prematurity</td>
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<td>Low-birth weight</td>
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<td>Female sex</td>
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Natural course of IH includes the following steps; they are frequently very small or even invisible at birth, show rapid growth during the first 6 months of life and growing may continue until 12 months in some instances, and exhibit a gradual regression after 1 year of age to 7-10 years. Spontaneous regression of IH are reported especially after 18 months of age. Thus, majority of hemangiomas in
infantile age group resolve spontaneously and only a small proportion of the cases with IH requires treatment.

**INDICATIONS FOR TREATMENT**

Because the majority of the patients (80-90%) with IH present with superficial or non-organ dysfunctioning lesions, the indications for treatment should be noted by clinicians. Generally accepted indications of treatment for IH are summarized as GLUT-ONE acronym in Table 3. GLUT-ONE acronym can help clinicians for the rapid decision of treatment. For the remaining cases the main tasks for the practitioners should be informing the family about the natural course and close follow-up with physical examination, sequential photographs or radiologic images of the lesion.

**Table 3. GLUT-ONE acronym depicting indications of treatment**

| Giant IH (with a potential of hematological or cardiac complications) |
| Liver and/or other visceral organ involvement (risk of Kasabach-Merritt syndrome) |
| Ulcerated or bleeding IH (neck, anal-genital-perineal zone, joints) |
| Threatening of life (laryngeal, upper airway lesions) |
| Nasal obstruction (nose) |
| Orbital or visual dysfunction (orbita) |
| Auditory disturbance (ear) |
| Upper gastrointestinal difficulty (lip, mouth) |
| Musculoskeletal difficulty (neck, shoulder, joints) |
| Non-localized IH (segmental, multifocal or systemic involvement) |
| Esthetic/cosmetic compromise (facial lesions) |

**STEROIDS**

The efficacy of systemic corticosteroids for the treatment of IH was first reported in 1967. Subsequently, oral or intravenous methylprednisolone (MPZ), and prednisone have become the mainstay treatment for hemangiomatous lesions in infants. Researchers have found that corticosteroids cause a pharmacologic ligation of tumoral vessels by increasing vascular sensitivity to circulating vascular agents and the transcription of interleukin-6, a proangiogenic cytokine, is significantly lowered by corticosteroids.

In cases with IH and Kasabach-Merritt syndrome resistant to conventional steroid treatment, high-dose MPZ (30-100 mg/kg/day starting dose) have been shown to be effective. However, the use of systemic corticosteroids is limited due to the potential for numerous side effects, including growth delay, cushingoid appearance, behavioral changes, irritability, gastrointestinal disturbance, hypertension, adrenal insufficiency, and compromised immunity. Intralesional corticosteroid injections, especially in patients with focal periocular hemangiomas, can be considered an alternative to systemic corticosteroid treatment. In selected cases with superficial IH good response with topical use of corticosteroids have been demonstrated.

**INTERFERON**

Interferon (IF) α-2a and α-2b have become therapeutic options for IH due to their antiangiogenic and antineoplastic properties, especially in cases that corticosteroids failed. Ezekowitz et al. reported that 90% of their cases with life-threatening hemangiomas exhibited marked regression after receiving IF α-2a subcutaneously. However, neurologic disturbances, such as spastic diplegia and motor development impairment, and other potential side effects such as fever, malaise, neutropenia, anemia, increase in liver transaminases, anorexia, weight loss, confusion, and insomnia limit the widespread use of IF. Another limitation of IF is its high cost, as compared to other therapeutic options, especially in developing countries with limited financial resources.

**CHEMOTHERAPEUTIC AGENTS**

After the discovery of high tubulin content and increased angiogenic activity in endothelial cells vincristin has been popular in treatment of IH.
Vincristin, a mitotic spindle poison, was demonstrated to be effective especially in management of steroid-resistant, life-threatening kaposiform hemangioendothelioma. Peripheral and autonomic neurotoxicity are among the side effects of vincristin. Another chemotherapeutic drug employed in treatment of IH is an alkylating agent, cyclophosphamide. It exerts its effect via blocking or decreasing the proliferation of new capillaries and good responses have been reported in treatment of steroid-resistant and life-threatening hepatic IH. Although cyclophosphamide has serious side effects potentially, such as hemorrhagic cystitis, infertility and secondary neoplasms, lower doses and short duration of therapy can avoid serious toxicity.

**IMIQUIMOD**

Imiquimod, an immune-response modifier has been shown to be effective in resolving IH by inducing local production of cytokines which are efficient in regression of vascular lesions such as interferon α, interleukin-6 and tumor necrosis factor. Like other topical agents, imiquimod is effective mostly in superficial IH and erythema and skin crusting are the frequently seen side effects.

**SIROLIMUS**

As an inhibitor of the mammalian target of rapamycin (mTOR) pathway the use of sirolimus provided benefit in treatment of IH. It targets the self-renewal and vascular differentiation potential in patient-derived hemangioma stem cells. Sirolimus appears to be effective and safe in patients with life-threatening vascular anomalies and represents an important tool in treatment of complicated vascular malformations and lymphatic malformations.

**PROPRANOLOL**

Antiproliferative effect of propranolol on severe IH was first described in 2008 in a group of patients. Nowadays, propranolol is the preferred choice of treatment for the IH requiring intervention. Rapid stabilization and involution of the problematic lesions with propranolol have made it the gold standard for the treatment of many ulcerated or function-impairing IH. Oral propranolol has been reported to be better than steroids in context of efficacy and less side effects were reported in a few study comparing propranolol and steroids.

**Mechanisms of Effect**

Obviously, the underlying mechanisms of effect of propranolol in IH have not been completely understood. Recent investigations have proposed a variety of mechanisms about the action of propranolol. Among them, pericyte-mediated vasoconstriction, inhibition of the neovascularization and catecholamine-mediated angiogenesis, induction of apoptosis in endothelial cells and inhibition of the renin-angiotensin system are included.

**Pretreatment requirements**

Children with bronchial asthma, arrhythmias, cardiac failure, hypotension, hypoglycemia and allergic to propranolol should not be treated with this β-blocking agent. In Table 4, pretreatment requirements for propranolol are summarized. Thyroid function tests are recommended in children with large cutaneous or hepatic IH, since increased levels of iodothyronine deiodinase in those lesions can cause hypothyroidism. Although pretreatment ECG was demonstrated to have a limited value for patients with an unremarkable cardiovascular history, normal heart rate and blood pressure in a recent cohort study, a baseline ECG is generally suggested. Similarly, ECHO is not an obligation but can be used to exclude structural of functional heart disease.

**Side effects**

Propranolol is a nonselective β-adrenergic antagonist and blocks both β₁- and β₂-adrenergic receptors competitively. Bradycardia, bronchoconstriction, hypotension, hyperkalemia and reduced physiological response to hypoglycemia are expected side effects of propranolol and cardiac assessment and monitorization of serum electrolytes and blood glucose levels are recommended before and during the therapy.

**Local Administration**

Oral administration of propranolol although effective, is also associated with systemic unwanted effects mentioned above. Treatment with local administration may provide efficacy with lower incidence of side effects. In a recent meta-analysis, authors have assessed the treatment results of IH with locally administered β-blockers and they have
found clinically significant response rate of 80% with topical administration of propranolol and timolol. Although topical β-blockers are efficient in treatment of superficial IH, lower efficacy in mixed and deep IH limits their widespread use.

Table 4. Requirements before propranolol treatment

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<td>Blood pressure</td>
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<td>Pulse rate</td>
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<td>Glucose</td>
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<tr>
<td>Electrolytes ± Thyroid function tests</td>
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<tr>
<td>Chest X-ray</td>
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<tr>
<td>Electrocardiogram ± Echocardiography</td>
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Duration

Optimal duration of treatment remains a problem due to risk of recurrence after the cessation of propranolol before the age of spontaneous regression, which is generally accepted as 18 months (8). Administration of propranolol at least until the age of 1 year is recommended to avoid relapses. However, some authors suggest that propranolol can be used in all stages of IH and report good clinical improvement even beyond proliferative phase.

Treatment Failure

Treatment failure with propranolol is reported in a small proportion of patients with IH. One of the probable reasons for poorer response or failure is advanced patient age beyond the proliferative phase of IH like 2 patients in our previous series. In a recent study, the authors have reported treatment failure in focal facial lesions twice as frequently as other types of IH but no histopathological reason has been identified to explain the failure.

CONCLUSION

The impressive discovery of efficacy of propranolol in treatment of IH represent an effective, inexpensive, readily available and safe therapeutic innovation for most of the cases with IH. In many centers propranolol has become the first line treatment option in treatment of IH. Large-scale phase III clinical trials are needed to determine optimal dosing for propranolol and long-term safety profiles. Optimal duration of treatment and treatment failure in some cases with propranolol remain as two major problems to be resolved. Future studies should be directed to answer the questions regarding the optimal duration of propranolol treatment to overcome recurrences and clinical and histopathological characteristics of IH that failed treatment with propranolol. GLUT-ONE acronym can assist clinicians to remember the indications for treatment as IH are GLUT-1 positive vascular tumors.

REFERENCES


