The Role of Beta Blockers and Combined Therapies to Treat Pediatric Hemangiomas

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Hemangiomas Of Infancy

Families Often Told Hemangioma Would “Go Away”

Why treat?
Prevent Potential Morbidity

Hemangiomas Of Infancy
Delayed Referral

Early Referral Is Essential!!
Oral Propranolol

Early referral
Prevention of progression

Late referral
Proptosis, ptosis
Bulky hemangioma
High output state
Will require surgery
Benefit Of Early Treatment

When To Treat

*** Encourage Early Referral from Pediatricians ***

Medical Management of Hemangiomas

- Which patients to treat medically
- When to treat
- How to treat
- How to monitor

Medical Management of Hemangiomas

- Location and size of hemangioma
- Superficial, subcutaneous or combined hemangioma
- Focal vs segmental hemangioma
- Single vs multiple lesions
- Associated symptoms – stridor, ulceration/pain/bleeding, ptosis/ambyopia/astigmatism, feeding

Treatment of Patients with Hemangiomas

- Observation
- Local therapy:
  - flashlamp pulsed dye laser
  - intralesional treatments
  - topical treatments
  - surgery
- Systemic therapy:
  - oral beta blocker therapy:
    - Propranolol, Hemangeol®, Nadolol, Atenolol
  - oral Corticosteroids
  - intravenous Vincristine
  - Interferon
- Combined therapies

Topical Beta Blocker

Begin Topical Beta Blocker

- 2 mo old
- 2 weeks later
- 5 months later

- 5 mo old
- 10 week premature ultrasound, pain
- 2 weeks later
- 5 weeks later

- 7 week old male
Beta Blockers: How do they work?

• Pre-therapy evaluation
• Initiation of therapy
• During therapy
• After therapy

Propranolol Accelerates Adipogenesis in Hemangioma Stem Cells and Causes Apoptosis of Hemangioma Endothelial Cells

How to monitor patients treated with systemic beta-blocker therapy

Is cardiovascular evaluation necessary prior to and during beta-blocker therapy for infantile hemangiomas?

Cardiac Screening in Infants with Infantile Hemangiomas before Propranolol Treatment

Propranolol is a nonselective beta blocker that has been used in children for more than 40 years for the treatment of:

- Supraventricular tachycardia
- Long QT syndrome
- Hyperdynamic cardiomypathy
- Hypoxic spells associated Tetralogy of Fallot
- Hypertension
- Tachycardia associated with thyrotoxicosis

Potential Cardiac Contraindications to Propranolol Use in Infants

- Congestive heart failure associated with cardiomypathy or myocarditis
- Second- or third-degree heart block with bradyarrhythmia
- Aortic coarctation and other causes of systemic outflow tract obstruction
- Other potential causes of myocardial ischemia (e.g., anomalous left coronary artery from the pulmonary artery)
- Hypotension of various causes
Initiation Of Therapy

Inpatient vs outpatient
Outpatient monitoring – what parameters and for how long?

Use of propranolol for treatment of infantile haemangiomas in an outpatient setting
Phillips et al. 2012 *J Paediatr Child Health*

Twenty-Four-Hour Hospitalization for Patients Initiating Systemic Propranolol Therapy for Infantile Hemangiomas—Is It Indicated?
Liu et al, 2013 *Pediatr Dermatol*

Conclusion:
This study suggests that 24-hour hospitalization with hemodynamic monitoring may not be necessary for safe initiation of propranolol therapy in otherwise healthy infants.

Parental education on frequent feedings to decrease the chance of hypoglycemia may be as effective as 24-hour hospitalization.

Oral Propranolol

Prevention of progression
Reversal of astigmatism, amblyopia

Combination Oral Beta Blocker And Pulsed Dye Laser

Propranolol Potential Side Effects

- Cool extremities
- Sleep disturbances
- Gastrointestinal symptoms
- Hypotension
- Bradycardia
- Hypoglycemia
- Bronchospasm
- Long-term effects

Monitoring after therapy

Neurodevelopment?
Developmental milestones?
Propranolol treatment of infantile hemangiomas does not negatively affect psychomotor development
Moyskine et al.

Especially in young children the possibility of long-term behavioral consequences of propranolol use has been a constant concern, but there have been no data other than purely theoretical considerations to support these.

Even if reporting of memory disorders or neurodevelopment defects by cardiologist could be underestimated, these side-effects have never been reported in over 40 years of use.

MEDICAL THERAPY FOR VASCULAR MALFORMATIONS

Supportive – pain management, antibiotics, bisphosphonates, corticosteroids

Anticoagulant – Lovenox
peri-procedural, travel, pregnancy

Antiplatelet/Anti-inflammatory – Aspirin, Ibuprofen

Past – Thalidomide, Celebrex, Marimastat

Present – mTor inhibitors – Sirolimus, Everolimus, Doxycyclin, Propranolol

MTOR INHIBITORS

Rationale for use:
- M-tor activation in vascular anomalies was observed in vivo
- Overexpression of Akt in endothelial cells causes vascular malformations in mice

Arbiser et al* found expression of a downstream target of Akt and mTOR signaling in vascular malformations, suggesting possible Rapamycin sensitivity, and provided a rationale for treating vascular malformations with mTor inhibitors such as Rapamycin

*Shirazi et al, Mammalian Target of Rapamycin (mTOR) is Activated in Cutaneous Vascular Malformations in Vivo. Lymph Res & Biol, 2007

Sirolimus
Rapamune®

Oral medication
Pharmacokinetics – therapeutic drug monitoring
Hypercholesterolemia
Mucositis
Lymphomarepression
Cancer susceptibility, especially skin cancer, lymphoma
Interactions with multiple prescription and nonprescription/herbal medications
Dosage escalation, drug level and biochemical monitoring – frequent blood tests

Topical medication

*A generic version of Rapamune tablet has been approved by the FDA
Sirolimus

- Kaposiform Hemangioendothelioma
- Lymphatic Malformations
- Kaposiform Lymphangiomatosis
- Generalized Lymphatic Anomaly
- Blue Rubber Bleb Nevus Syndrome
  - (histology demonstrates lymphatics)
- ?Venous Malformations
- ?HHT
- ?Other

Sirolimus for Extensive Lymphatic Malformation

Pre-Treatment

6 months Sirolimus

Thank you

SIROLIMUS

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Concerns</th>
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<tbody>
<tr>
<td>Oral administration</td>
<td>Short and long-term toxicities</td>
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<tr>
<td>Improved quality of life</td>
<td>Unclear duration of treatment/endpoint</td>
</tr>
<tr>
<td>Improved laboratory parameters</td>
<td>Unclear optimal dose</td>
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<tr>
<td>Single agent (e.g. KHE)</td>
<td>Frequent blood tests required</td>
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<tr>
<td>Very effective for certain diagnoses</td>
<td>Resistance</td>
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There will likely be improved medications in the future