Use of Propranolol in Infantile Hemangioma

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Propranolol, is a nonselective beta-blocker and if not contraindicated, stands as the first-line agent for hemangiomas that impair function or cause permanent disfigurement.[1] In 2014, propranolol hydrochloride oral solution was approved by the US Food and Drug Administration for the treatment of proliferating infantile hemangioma (IH) requiring systemic therapy.[2]

Propranolol inhibits the growth and induces regression of IHs by its potential mechanisms of inducing vasoconstriction, decreased expression of vascular endothelial growth factor and matrix metalloproteinases, and/or triggering of apoptosis.[3-5]

The goals of hemangioma treatment include:
• Prevention or reversal of life-threatening or function-threatening complications
• Prevention or minimization of disfigurement from residual skin changes
• Minimization of psychosocial distress for the patient and family
• Adequate treatment of ulceration to minimize scarring, bleeding, infection, and pain.

When will you think of administering propranolol in infantile hemangioma?
I will administer propranolol for IH on and around eyelids, lips, tip of the nose, and anogenital region for sure. Large proliferating IH, multiple IH, and segmental IH will all make me think of oral propranolol. The principle is IH affecting vital structures and IH prone to complications such as scarring and ulceration need medical intervention. With the safety and efficacy, we have experienced, we are willing to offer many more patients' propranolol to improve the quality of life and have minimal residual sequelae.

In which phase of hemangioma would you prescribe propranolol?
I would prescribe propranolol during any phase. There are some recent papers where it has been shown that propranolol works in IH well beyond the proliferation phase. Even IH in 6 and 8-year-old children have shrunk following propranolol. Hence, if surgery is being considered for residual hemangioma, it is worth trying oral propranolol for a few months prior, for a better cosmetic result.

As per the published literature, oral propranolol has been used to treat IHs beyond the proliferative phase. In a multicentric, retrospective study, 42 children aged 7 months to 10 years with documented cessation of hemangioma growth were treated with propranolol 1.5–3 mg/kg/day for 1–8 months. In all children, the rate of involution increased with propranolol compared with the rate of involution during active nonintervention before treatment.[6,7]

What is the infantile hemangioma where one would avoid the use of propranolol?
One must be careful using propranolol in cases of posterior fossa malformations – hemangiomas – arterial abnormalities – cardiac defects – eye abnormalities – sternal cleft and supraumbilical raphe syndrome (PHACES syndrome) since potentially hypoperfusion of the brain is a small possibility. We have used it successfully in two cases of PHACES syndrome. Mandibular and neck IH may be associated with subglottic hemangiomas and may sometimes be resistant to oral propranolol. Sometimes, combination with steroids and occasionally surgical intervention may be required for worsening stridor.

Literature mentions that contraindications to the use of propranolol are cardiogenic shock, documented chronic and significant sinus bradycardia, documented chronic and significant hypotension,

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greater than first-degree heart block, heart failure, history of bronchospasm or wheezing, hypersensitivity to propranolol, and preterm infants with corrected age <5 weeks (postnatal age in weeks minus number of weeks preterm).

What would the pretreatment investigations be for infantile hemangioma where we intend to start propranolol?

Evaluation is mainly clinical. Avoid propranolol in premature infants, low birth infants, and infants with heart rate <80 beats/min. In a study involving 163 patients, Yarbrough et al. observed that pretreatment electrocardiograms (ECGs) did not predict or prevent any adverse events.[8]

As per conventional literature, the pretreatment evaluation should include:

- History: Directed to rule out the cardiovascular and respiratory abnormalities (e.g., poor feeding, dyspnea, tachypnea, diaphoresis, wheezing, heart murmur, and family history of heart block or arrhythmia)
- Physical examination: Cardiac or pulmonary assessment and measurement of heart rate and blood pressure.

ECG is indicated in children with:

- Heart rate lower than normal for age
- History of arrhythmia or arrhythmia detected during examination
- Family history of congenital heart disease or maternal history of connective tissue disease.

Imaging studies including cardiac ultrasound or cardiac magnetic resonance imaging (MRI) should be obtained in children with large facial hemangiomas at risk for PHACES to rule out the possibility of severe aortic coarctation, which is a contraindication for propranolol use. In these patients, baseline head and neck MRI with angiography is also preferred before propranolol unless the clinical situation requires urgent treatment (e.g., severe visual obstruction due to an orbital hemangioma). In such cases, propranolol can be initiated at a lower dose and slowly titrated up to a maximum dose of 1 mg/kg/day.

Table 1: Side effects of propranolol use in hemangioma

| Serious adverse effects |
|-------------------------|
| Hypotension             |
| Bradycardia             |
| Hyperkalemia            |
| Bronchospasm            |
| Hypoglycemia            |

| Common side effects     |
|-------------------------|
| Restless sleep          |
| Constipation            |
| Diarrhea                |
| Cold extremities        |

The most worrisome. Sweating is the only sign of hypoglycemia that is not blocked by a beta-blocker. Hence, sweating may be the most reliable early sign of hypoglycemia to watch for. Routine screening of serum glucose is not indicated because timing of hypoglycemic events is variable and unpredictable. Hence, to reduce the risk, propranolol should be administered during daytime hours with a feed just shortly before or after administration and should be discontinued in periods of poor oral intake or illness.

In a review of 906 French children (median age 114 days) treated with propranolol for complicated hemangiomas, one or more adverse effects occurred in 81 (9%). Serious adverse effects occurred in 24 patients (2.6%) with cardiac events in two patients, respiratory events in nine, and hypoglycemia in four patients. Common adverse effects were sleep disturbances, acrocyanosis, and diarrhea.[9]

Do you admit all patients before starting propranolol? When would refer to the pediatrician before starting propranolol?

We mostly use propranolol on an outpatient basis. Admission is only for high-risk infants and infants <2 months of age. I normally prefer to keep the pediatrician in the picture right from when I plan to start propranolol and throughout the course.

According to many authors, especially in older studies, initial hospitalization of children with IH who need to be administered propranolol is mandatory. Other authors, especially in the newer studies, believe propranolol is a relatively safe drug for use in IH, routine cardiac screening, estimation of blood glucose for all infants before initiating propranolol, and overzealous monitoring of the children while on therapy is unnecessary.[10] Only selected cases should undergo such detailed tests and others may be treated on an outpatient basis with gradually escalating the dose of propranolol.

Hospitalization for initiation of oral propranolol can be considered in the following circumstances:

- Infants ≤5 weeks of age
- Preterm infants with corrected age ≥5 weeks (postnatal age in weeks minus number of weeks preterm)
- Infants of any age with comorbid conditions affecting...
the cardiovascular and respiratory system including symptomatic airway hemangiomas
• Infants of any age with conditions affecting blood glucose maintenance.

What is the monitoring required after starting propranolol?

Monitoring is mainly pulse and blood pressure for 2 h after starting propranolol, and every time the dose is increased. We reevaluate patients every week for the first 2 weeks, then every fortnight for 2 months and every month thereafter as per literature.

Since the effect of oral propranolol peaks at 1–3 h after administration, it is recommended that patients are monitored with measurement of heart rate and blood pressure at 1 and 2 h after the initial dose and after every dose increase of 0.5 mg/kg/day. However, in clinical practice, many experts do not monitor heart rate and blood pressure in clinic after first dose and after every dose increase.

What are the instructions given to the parents while administering propranolol?

First thing I tell the parents is to rush the child to the pediatrician or the closest hospital in case of coldness, shakiness, increased sweating, and excessive drowsiness. I also emphasize that the side effect one has to worry the most about during propranolol treatment is low blood sugar. She must administer propranolol shortly after a feed. Feeds should be frequent, and child should not be without a feed for more than 6 h. The last dose of propranolol should be around 7 pm. Skip the dose if a meal is skipped or if the baby is not feeding well or in case of vomiting. Please refer to instruction list or practical tips for the patient as mentioned in Box 1.

At what dose should propranolol be initiated? And how the dose should be escalated?

I start propranolol at 1 mg/kg/day in three divided doses. I reevaluate after 1 week, and if the child is tolerating it well, the dose is increased to 2 mg/kg/day and this dose is continued throughout the course.

The usual dosage of propranolol in IH is 2 mg/kg/day. Some authors recommend a lower starting dose and gradual dose escalation, for example, 0.5 mg/kg/day divided into three daily doses for 1 week, followed by 1 mg/kg/day for 1 week and thereafter the optimal dose of 2 mg/kg/day.

How would you dispense propranolol?

We hand over 10 mg tablets to our pharmacist who triturates and prepares the 0.33 or 0.66 mg dose packets. These are mixed with rose syrup or honey and administered to the child.

Alternatively, propranolol solution 2 mg/ml can be compounded by the pharmacist as follows:
• Propranolol hydrochloride 0.02 g
• Sodium benzoate 0.05 g
• Citrate phosphate (CP) buffer 50.0 ml.
• Sucrose syrup (64% w/w) to make 100.0 ml

0.2 g propranolol hydrochloride and 0.05 g of sodium benzoate are dissolved in 50 ml of CP buffer solution and then make up the total volume of 100 ml with sucrose syrup.

Should propranolol be tapered off or can it be abruptly stopped?

According to literature, while stopping propranolol, the dose should be reduced gradually over a period of 2 weeks. Cardiac complications may occur up to 2 weeks (maximum within 4–8 days) after stopping the drug.\(^{[11]}\)

In our cohort, we have abruptly discontinued propranolol without any untoward effects or rebound growth.

When would one think of discontinuing propranolol?

Oral propranolol should be given till the baby is 12–15 months old irrespective of how old the infant was when propranolol was started. In more than fifty children with IH, we have treated so far; we have not yet encountered a situation when we had to discontinue propranolol due to side effects.

Have you seen relapses after stopping propranolol?

We used to see relapses when we used to stop propranolol after a course of <6 months. The relapse was mainly in the form of slight increase in thickness and redness of the IH. This responds readily to reintroduction of propranolol.

On review of literature, rebound growth after propranolol discontinuation has been seen in approximately 14%–25% children. The risk factors for relapse are ill understood till date.

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**Box 1: Few practical tips for the use of propranolol in infantile hemangioma**

- Administer propranolol during daytime only
- Administer propranolol only after feeds
- Frequent feeds are advisable. The baby should not go without feed for >6 h
- If the baby refuses feeds, you can skip the propranolol dose
- Administer the exact dose prescribed by the doctor
- Doses should be at least 6 h apart
- If the baby spits out a dose or there is uncertainty of how much medicine went in, just wait for the next dose
- If you miss administering one dose, do not double or increase the next dose
- If the child is sick or not eating adequately stop propranolol and see the pediatrician. Do not restart propranolol unless advised by the pediatrician
although there is some evidence that administering propranolol for a longer duration diminishes the likelihood.\textsuperscript{12,13}

In a single institution study including 158 children with hemangiomas located predominantly in the head and neck region who were treated with propranolol for 3–12 months, a relapse occurred in 40 (25%), 0.5–5 months after treatment was started. In half of them, the relapse was mild and did not require retreatment. Factors associated with an increased risk of relapse included segmental distribution and depth of hemangioma.\textsuperscript{13}

How long should one typically give propranolol?
A study by Gianchetti showed that 12 month treatment with propranolol was associated with a lower relapse rate.\textsuperscript{14} The duration of administering propranolol may have to be decided on a case-to-case basis. As per literature, children with IHs treated with propranolol should be followed up at 1–3-month intervals for response assessment and dose assessment for weight gain. The duration of treatment typically ranges between 6 and 12 months or until the child is a 12–18 month old but maybe longer, depending on the size and location of hemangioma and response to treatment.\textsuperscript{1}

What if the response to oral propranolol at the end of 4 months is not as much as expected?
The first thing to do is recheck the child’s weight and confirm that the dose of 2 mg/kg/day as per current weight is being administered. Often the child is receiving the same dose in the last 2–3 months despite weight gain. If response to propranolol 2 mg/kg/day is insufficient, one can increase the dose to 3 mg/kg/day. We had to use the higher propranolol dose in a case of mandibular and neck IH with worsening stridor. The deeper component in mixed IH responds more slowly and less completely than the superficial one.

When would one label hemangiomas resistant to propranolol?
After starting propranolol, the IH typically becomes softer and the color lighter within 48 h. IH growth stops within 24 h to 2 weeks at the most. If after 2 weeks, the IH continues to grow, one would label it propranolol resistant. Most case reports of propranolol-resistant IH are subglottic.

Literature review suggests that lack of response to treatment with propranolol is rare. In a French retrospective, multicenter study including 1130 children treated with propranolol and 10 (0.9%) had propranolol resistant hemangiomas. Resistance was defined as continued growth during proliferative phase or no involution during the postproliferative stage after >4 weeks of oral propranolol at ≥2 mg/kg/day. Five of the ten children who did not respond to propranolol had hemangiomas in the postproliferative stage and were older than 8 months at the start of treatment. Three children with hemangiomas in the proliferative stage showed rapid response to adjuvant systemic corticosteroids.\textsuperscript{15}

Any experience with newer beta blockers in management of hemangiomas?
I have no experience with oral beta-blockers other than propranolol. To my knowledge, a few trials suggest that nadolol, atenolol, acibutolol, and labetalol may be as effective as propranolol for the treatment of proliferative hemangiomas potentially with a lower rate of adverse effects such as bronchoactivity and sleep disturbances.\textsuperscript{16,17} However, these findings are preliminary and need to be confirmed by larger clinical trials.

What are the treatments that can be combined with propranolol?
In the rare situation that propranolol alone is not sufficient, oral or intralesional steroids can be added. Fortunately, I have not faced such a predicament.

Have you used propranolol in hemangiomas other than infantile hemangiomas?
I have not and based on current literature; I suggest no practitioner should. There have been anecdotal reports of propranolol in congenital hemangiomas (especially visceral) and lymphatic malformations with variable success.\textsuperscript{18-20} As of now, propranolol is approved only for treatment of IH.

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Conflicts of interest
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