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# Consensus Statement for the Treatment of Infantile Haemangiomas with Propranolol

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## **Consensus Statement for the Treatment of Infantile Haemangiomas with Propranolol**

### **Abstract**

Although the majority of infantile haemangiomas do not require treatment due to a natural history of spontaneous involution, some require early intervention. The Australasian Vascular Anomalies Network and the Australasian Paediatric Dermatology Network have developed a consensus statement for the treatment of infantile haemangiomas with oral propranolol.

Infants with haemangiomas that are life-threatening, at risk of ulceration, or at risk of causing significant functional impairment, psychological impact or physical deformity should be treated early with oral propranolol. Oral propranolol is safe and effective, and in most healthy infants, oral propranolol can be started in an outpatient setting.

**Key words:** Australian, New Zealand, infantile haemangioma, hemangioma, propranolol, beta-blocker, consensus, vascular anomalies

### **Abbreviations**

AustPaedDerm Australasian Paediatric Dermatology Network

AVAN Australasian Vascular Anomalies Network

MRI/MRA magnetic resonance imaging/ magnetic resonance angiography

PHACE                      Posterior fossa brain malformations, **H**aemangiomas, **A**rterial anomalies , **C**ardiac anomalies (and Coarctation of the aorta), **E**ye or Endocrine abnormalities

## **Introduction**

Infantile haemangiomas are the most common tumours of infancy, regularly encountered in dermatology and paediatric practices. Due to the natural history of spontaneous involution, the majority of haemangiomas do not require treatment. However, some haemangiomas may compromise vision, hearing, or breathing or cause complications such as ulceration or cosmetic disfigurement. Since the first published report of infantile haemangioma responding to propranolol in 2008<sup>1</sup>, propranolol has become the treatment of choice when systemic therapy is required. The exact mechanism of its action in haemangiomas has not been fully established, and has been proposed to be a complex interplay of the promotion of pericyte-mediated vasoconstriction, the inhibition of vasculogenesis and catecholamine-induced angiogenesis, the disruption of haemodynamic force-induced cell survival, and the inactivation of the renin–angiotensin system.<sup>2</sup>

Despite initial concerns regarding clinical safety, recent literature suggests that for most patients propranolol is safe, well tolerated and effective.<sup>3-7</sup> A recent randomized controlled trial concluded that propranolol is both effective and safe when compared to placebo. Propranolol has become the accepted treatment for infantile haemangiomas.<sup>8</sup>

The aim of this consensus statement is to provide a guide to the safe and effective use of propranolol for infantile haemangioma.

## **Methods**

Over a twelve-month period, members of the Australasian Vascular Anomalies Network (AVAN) and the Australasian Paediatric Dermatology Group (AustPaedDerm), developed a framework for the treatment of infantile haemangiomas with oral propranolol in the Australian/New Zealand context.

Members of these two groups include paediatric dermatologists, paediatricians, oncologists, plastic surgeons and specialists from several other disciplines in Australia and New Zealand. Following review of the literature, sharing of clinical experience, discussion and debate, a consensus statement for treatment with propranolol was developed.

## **Rationale for treatment**

Infantile haemangiomas are benign tumours comprising of proliferating vascular endothelial cells, which usually appear at or shortly after birth, and can grow rapidly. They usually stop growing by six months of age, but larger haemangiomas may continue to grow for 18 months. Thereafter haemangiomas slowly reduce in size, but have largely stopped involuting by five years of age, sometimes leaving permanent telangiectasia, scarring (particularly following ulceration) or excess fibro-fatty tissue (usually in haemangiomas which had deep and superficial components).<sup>9</sup>

Many health professionals tell parents that their child's haemangioma will go away within a few years. This is often misleading and sometimes wrong. Without treatment, around one third of haemangiomas cause some permanent skin changes, and 10% are associated with long-term changes that can impact on a child's development and socialisation.

Early treatment with propranolol can significantly reduce the likelihood and severity of these complications.<sup>8</sup> Infants with haemangiomas that are likely to cause permanent problems should be treated as early as possible and/or referred for urgent evaluation within days (not weeks).

In some cases, other benign tumours, cancers or vascular anomalies can masquerade as infantile haemangioma. If the diagnosis is unclear, a referral for an expert opinion should be made before commencement of propranolol.<sup>10,11</sup>

## **Indications for treatment (Figure 1)**

1. *Life or function-threatening infantile haemangiomas*
  - a. Airway haemangioma

- b. Visual impairment (risk of amblyopia from visual obstruction or pressure induced astigmatism)
  - c. Spinal cord involvement
  - d. High flow haemangioma with cardiac compromise – e.g. large hepatic lesions
  - e. Haemangiomas causing hypothyroidism
  - f. Large haemangiomas interfering with physical development
  - g. Systemic haemangiomatosis
2. *Ulcerated haemangiomas with significant pain*
- a. If inadequate response to standard wound care, consider propranolol or laser treatment or early surgery in addition to propranolol
3. *Haemangiomas at significant risk of ulceration*
- a. Lip
  - b. Perineum
4. *Haemangiomas with significant risk of deformity and/or psychosocial impact*
- a. Short term - parents not interacting normally with their infant despite adequate explanation
  - b. Medium term - many untreated haemangiomas will still be visible at 3-8 years of age. Psychosocial adverse effects may develop before this age, so consider early treatment
  - c. Long term - haemangiomas can leave permanent changes including deformity, scarring, atrophy, telangiectasia and redundant skin. High risk areas include lips, nose, cheeks and ears - where surgical repair can be difficult. Permanent nasal cartilage deformity is common with untreated nasal tip lesions. Haemangiomas with a 'step-edge' or cobblestone surface often leave permanent changes

## **Early treatment options**

1. Oral propranolol

The first line therapy for infantile haemangiomas that warrant treatment is oral propranolol (or an alternate beta-blocker therapy).

## 2. Topical beta-blocker

Treatment with a topical beta-blocker may benefit some superficial haemangiomas. Topical beta-blockers are less effective than oral beta-blockers in the treatment of infantile haemangioma and should not replace systemic therapy in patients who have a clear indication for treatment. The most commonly used topical beta-blocker is timolol maleate 0.5% gel forming drops, one drop, applied to the lesion twice a day. Systemic absorption of topical timolol is variable but may be significant with ulcerated lesions, large lesions or in infantile haemangiomas affecting premature or small infants.<sup>12</sup>

## 3. Other medical treatment

- a. High dose systemic steroids (2 mg/kg/day) were commonly used in the past,<sup>13,14</sup> but are no longer first line therapy. They may be considered in patients in whom oral beta-blockers are contraindicated or ineffective.
- b. Other treatments include oral sirolimus, intravenous vincristine and oral angiotensin converting enzyme inhibitors, but efficacy and safety data are limited.

## 4. Surgery

Most infants with haemangiomas do not warrant surgery. However, surgery, with or without oral propranolol, can be an effective treatment for localised ulcerated lesions and lesions where significant psychosocial effects might be minimised by early surgery.

## 5. Laser

Early pulsed-dye laser therapy can be of benefit in flat haemangiomas. Laser may also be of benefit in ulcerated lesions not responsive to appropriate dressings.

## **Relative Contraindications for Propranolol – consider specialist advice in these circumstances**

1. Infants prone to hypoglycaemia: e.g. failure to thrive, concurrent/prior prednisolone therapy, poor feeding, gastroenteritis
2. Infants with cardiovascular disease, including conduction abnormalities
  - a. Persistent bradycardia <100 beats per minute if infant is under three months of age, and <90 beats per minute for infants 3-6 months of age
  - b. Coarctation of the aorta
3. Bronchospasm
4. Intracranial arterial anomalies (e.g. those seen in PHACE syndrome: **P**osterior fossa brain malformations, **H**aemangiomas, **A**rterial anomalies, **C**ardiac anomalies (and Coarctation of the aorta), **E**ye or Endocrine abnormalities).
5. Other systemic disease

## **Adverse effects of Propranolol (Table/Box 1)**

1. Less serious adverse effects
  - a. Sleep disturbance (wakefulness/somnolence). If persistent, consider dose adjustment or changing to atenolol
  - b. Cold extremities
  - c. Diarrhoea
2. Serious adverse effects (uncommon)
  - a. Hypoglycaemic episodes / seizures
  - b. Propranolol can aggravate hypoglycaemia in children, especially in the case of fasting, vomiting or overdose
  - c. Bradycardia and hypotension
  - d. Bronchospasm e.g. during an intercurrent respiratory illness

There is no current evidence in humans that propranolol taken in infancy or childhood adversely affects neurocognitive development.<sup>15-18</sup>

## **Timing of therapy**

Treatment should be initiated before permanent skin changes develop. Treatment should ideally be started in the first weeks or months of life, preferably early in the proliferative phase. As it is difficult to predict which lesions will proliferate significantly, close clinical monitoring during the proliferative phase may be required.

## **Assessment before starting propranolol**

A thorough medical history and clinical examination, including heart rate, are essential. Additional investigations are indicated only as determined by history and/or clinical examination.<sup>19</sup>

Particular caution and further investigation may be appropriate in the following situations:

1. Haemangiomas in a beard distribution – these may be associated with airway involvement. Consider indirect laryngoscopy
2. Segmental head and neck infantile haemangiomas which are at increased risk of PHACE syndrome. Consider echocardiogram, MRI/MRA of the head, and ophthalmology assessment
3. Segmental lumbar and pelvic haemangiomas - these can be associated with anogenital, renal or spinal anomalies. Consider ultrasound or MRI spine, and renal ultrasound
4. Infants with more than four infantile haemangiomas. Consider abdominal ultrasound, and/or ultrasound/MRI of the head
5. Large infantile haemangiomas can be associated with hypothyroidism and/or high output cardiac failure

## **Propranolol dosing and monitoring**

In thriving, healthy infants, oral propranolol can be commenced in an outpatient setting, with the first dose given at home.

Start propranolol at a dose of 1-2mg/kg/day (in two divided doses taken 8-12 hours apart). Increase to 2mg/kg/day after 1-2 weeks, unless a lower dose is clinically effective

1. In smaller infants (aged 0-4 weeks corrected and/or small for gestational age, or less than 2.5 kg body weight) and in infants with other clinical concerns (e.g. risk for hypoglycaemia) consider:
  - a. initiation of therapy as an inpatient
  - b. lower initial dose (e.g. 0.5 mg/kg/day)
  - c. splitting the daily dose into three rather than two doses
  - d. more gradual dosage escalation
2. In these higher risk babies, consider monitoring heart rate hourly for 3-hours and measuring glucose 3-hours following the initial dose and after any subsequent dosage increases.
3. Lower doses, and doses given three times a day may also be preferred in other settings, e.g. head/neck arterial dysplasia.
4. All parents should receive written instructions to cease propranolol if their child is unwell or not feeding normally – see Box 2.

### **Propranolol availability**

At the time of publication, a commercial preparation of propranolol for infants (Hemangirol, Pierre Fabre Laboratories, France) is available in Australia (not New Zealand) and can be prescribed. It is not presently listed on the Pharmaceutical Benefit Schedule (PBS). Alternatively, parents can dissolve commercially available propranolol tablets or use a compounded syrup preparation made up by a pharmacy. Older infants can usually take propranolol tablets.

Propranolol liquid is available fully funded in New Zealand through the Special Authority System (<http://www.pharmac.govt.nz/patients/SAForms>) for children < 12 years of age with haemangiomas at risk of functional impairment.

## Monitoring treatment

1. For most infants, monthly clinical monitoring is recommended until the lesion shows clear signs of involution, then every three months until cessation of treatment. In some situations, such as ulceration or enlarging facial lesions, more frequent initial monitoring may be required.
2. If the haemangioma responds well to treatment, it may be unnecessary to increase the dosage of propranolol as the child's weight increases.
3. If the response is inadequate, consider increasing the dosage of propranolol to 3 mg/kg/day (i.e. 1.5 mg/kg twice daily), and/or refer to a vascular anomalies specialist.

## Cessation of treatment

The optimal treatment duration with propranolol has not yet been established and may vary from 3 – 24 months. The aim of treatment is to switch off the proliferative phase of the haemangioma. Propranolol can be stopped safely without the need for weaning the dosage. Up to a quarter of haemangiomas will show rebound growth after treatment discontinuation.<sup>20</sup> This is often minimal and temporary. If rebound growth is significant, consider restarting propranolol at the previous dosage.

## Conclusion

Propranolol is effective in the treatment of infantile haemangiomas. This consensus statement draws upon the clinical knowledge of multiple specialists in vascular anomalies and paediatric dermatology and provides guidance for clinicians treating infantile haemangiomas.

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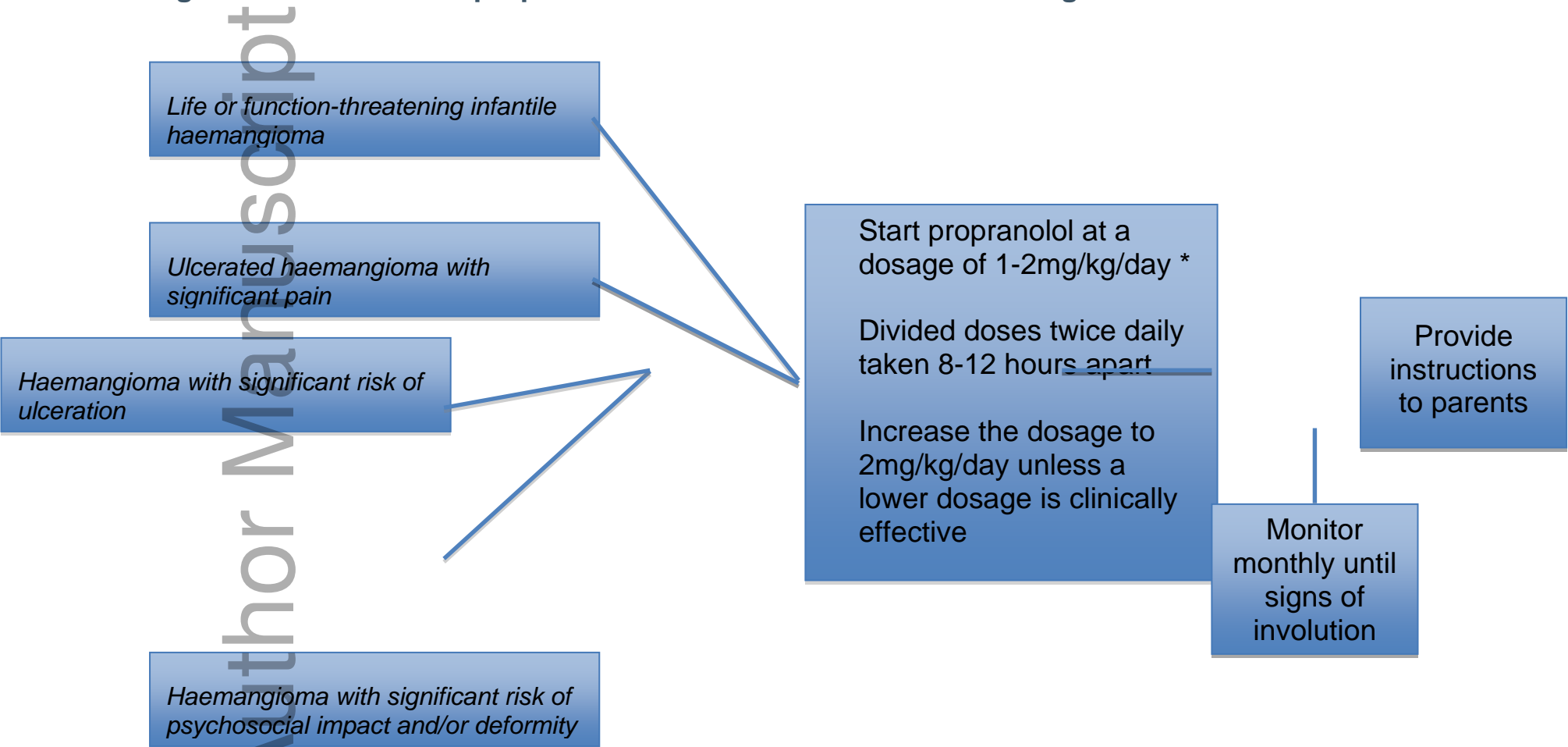
## Figure Legends

Figure 1: Guidelines of propranolol treatment for infantile haemangiomas

Box 1: Potential adverse effects of propranolol at the recommended dosage for the treatment of infantile haemangiomas

Box 2: Instructions for parents of infants being treated with propranolol for infantile haemangiomas

Figure 1: Guidelines of propranolol treatment for infantile haemangiomas



\* For high-risk and/or small infants refer to text

Monitor 3-monthly until cessation of treatment