# Use of Propranolol for the Treatment of Large Infantile Haemangiomas—A Report of Two Cases and Review of the Literature

**Dear Editor,**

Infantile haemangioma (IH) is the most common, benign vascular tumour of infancy.[1] Typically, IH goes through a proliferative phase in infancy, followed by involution over several years.[2] Watchful waiting is the best management with the natural history of spontaneous involution. For more than 4 decades, systemic corticosteroids remained the mainstay of treatment for large IHs; however, not only is the safety profile far from ideal, but the response to treatment is unpredictable and rebound growth does occur upon cessation of treatment.[1] Recent reports on the efficacy and safety of propranolol catapulted the use of this treatment of IH to the first-line status.[3] We describe 2 cases of large IHs treated successfully with oral propranolol.

## Case 1

A 2-month-old healthy Malay girl presented with a bright red tumour, having an irregular, hummocky surface over the upper half of the right face and scalp. She was born at term and noted to have a light purplish discolouration over the right temporal area, eyelid, nose and the lips. The vascular lesion rapidly grew in size over a period of 5 weeks, causing her to be unable to open the right eye, bleed from the right nostril with nasal blockage and difficulty to suck. She was treated elsewhere with oral prednisolone, at a dose of 2.5 mg/kg/day for 2 weeks followed by 3 mg/kg/day for 2 weeks with no response. The examination revealed a bright red tumour mass across the right side of the face, extending from the fronto-temporo-parietal area of the scalp, the upper eyelid with palpebral occlusion, upper part of the maxillary area of the face, the bridge of the nose, both ala nasi and the right side of the upper lip (Fig.1A). No ulcers or haemorrhagic areas were noted externally. Ophthalmological examination showed the extension of IH into the right upper eyelid, with none into the orbit.

We developed an IH management protocol (Table 1) to optimise safety, which included a pre-treatment screening and follow-up plan along with a propranolol regimen as per St Louis University School of Medicine, USA.[4] She was admitted at the age of 2.5 months to the hospital, for initiating the treatment. Pre-treatment screening was unremarkable. Magnetic resonance imaging (MRI) scan of the brain was normal. The initial response to propranolol was noted within 48 hours, with a noticeable reduction in size, softening of the tumour and a change of colour from intense red to purple. The patient was discharged after 48 hours of observation and the treatment was continued at home.

The child was reviewed for clinical assessment, treatment compliance and tolerance. After 2 weeks of treatment, the haemangioma showed a reduction in size and was able to open her right eye (Fig.1B). Following 3 months of treatment, the haemangioma showed remarkable reduction in size and appearance (Fig.1C). She was reviewed after 10 months of treatment and the IH had completely regressed (Fig.1D). Propranolol was tapered off over the subsequent 2 weeks. No propranolol-related side-effects were noted.

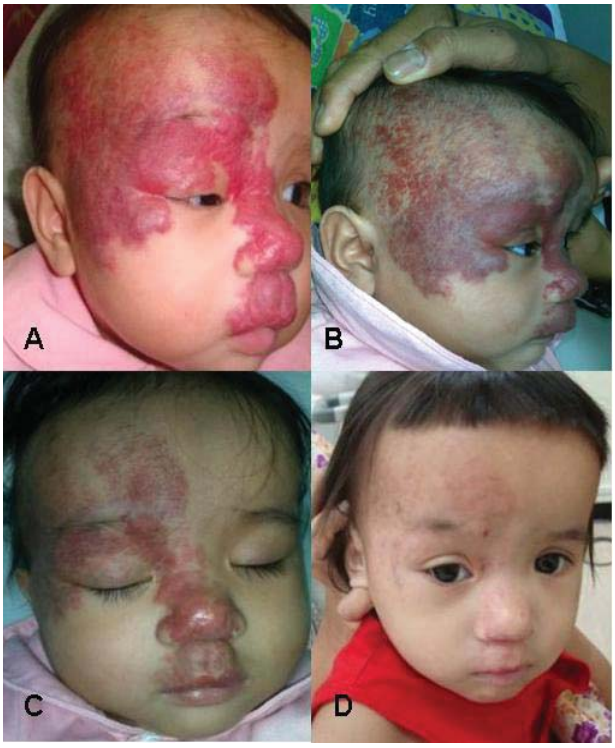


Fig.1. Case 1 with the large facial IH (A) before treatment, (B) after 2 weeks, (C) 3 months, and (D) 10 months of treatment.

Table 1.Protocol for Management of IH

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| • Patient – History of transient or prolonged hypoglycaemia in neonatal period, cardiac disease and atopy |
| • Family history of cardiac arrhythmia, autoimmune disease e.g. SLE |
| • Blood glucose |
| • Full blood count, liver function test and renal panel |
| • X-ray – Chest for cardiomegaly and lung diseases |
| • Cardiac evaluation – (Paediatric Cardiologist) - heart rate and blood pressure monitoring, electrocardiogram and echocardiogram |
| • Head and neck IH – Eye examination, ultrasound head/MRI/CT scan of the brain |
| • Ultrasound examination of the abdomen for hepatic haemangiomas |
| • Parent counselling and consent for propranolol treatment |
| • Oral Propranolol – Admit to Paediatric ward. Initial dose – 0.16 mg/kg every 8 hours. If vitals and blood sugar are stable the dose is doubled after every two doses up to a maximum of 0.67 mg/kg per dose (maximum total daily dose of 2 mg/kg). Discharge after 48 hours observation if vital signs and blood sugars are stable |
| • Follow-up – First review after 2 weeks and subsequent visits every month |
| • Direct access to the paediatric ward in case of any emergency |

CT: Computed tomography; SLE: Systemic lupus erythematosus

## Case 2

A 3-month-old healthy Malay boy was seen with a rapidly growing haemangioma of the left forearm. It was noted at birth as a light red, elevated lesion. The haemangioma extended from the distal half of the left forearm to the dorsum of the hand and proximal thumb (Fig. 2A). His left wrist and hand functions were unaffected. He was treated with oral prednisolone at a daily dosage of 2.5 mg/kg/day for 3 weeks at the referring facility, with negligible response.

Parent's concern of trauma, bleed and disfigurement were discussed and they were given the option of treatment with propranolol. A pre-treatment screening was done and was unremarkable. The patient was admitted to the hospital at the age of 3.5 months and started on oral propranolol as per the protocol. Colour change and softening were noted after 72 hours of the initiation of treatment. He was discharged home after 2 days on propranolol. The large IH continued to improve with respect to colour and thickness, as shown in the photograph taken after 6 months of treatment (Fig. 2B). The IH continued to regress when reviewed after 9 months of treatment. No adverse effects related to propranolol have been noted.

## Discussion

IH is the most common tumour in infants with a reported incidence of 4% to 10%.[1] The incidence is higher (22% to 30%) in extreme low birth weight babies. IH is more often found in the face (40%) and neck (20%) regions. Predisposing factors for IH include caucasian ethnicity, female sex and advanced maternal age.[5] Most (70% to 80%) of the IHs can be left untreated and allowed to follow its natural course.[2]

Mulliken and Glowacki[6] classified vascular anomalies into vascular tumours and vascular malformations. IH belongs to the group of vascular tumours. IH may not be obvious at birth and can be very small, before growing progressively. IH can be focal or segmental; single or diffuse; or superficial or deep. Another subtype of the vascular tumour is congenital haemangiomas (CH). CH are fully developed at birth and do not undergo more than proportional postnatal growth.[1]

The inheritance of IH is usually sporadic. In 2000, North et al[7] published their observation that, unlike other vascular tumours, IHs stain with the immunohistochemical marker

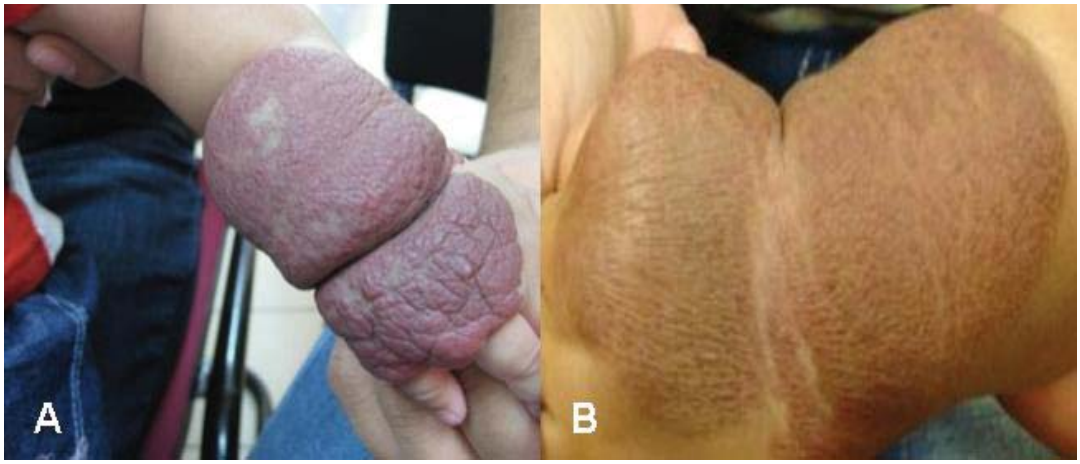


Fig.2. Case 2 with the large IH of the left forearm (A) before treatment, and (B) after 6 months of treatment.

GLUT. Other markers such as merosin, and LeY are present in haemangiomas, as well as in placental tissues, while being spared in other body tissues. The presence of these markers supported a placental-embolic theory, where an increased incidence of haemangioma was reported in infants born to mothers who have undergone chorionic villous sampling.[1,7] Regulators of growth and involution of haemangioma are poorly understood. During the growth phase, the basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) are the 2 major pro-angiogenic factors involved. Apoptosis occurs during the involution phase.[8]

IHs grow intermittently through infancy. The growth proceeds through the proliferative phase during the first 9 to 12 months of life, followed by quiescence of a variable period, and then involution, which may last for several years.[1] Ulceration does occur in rapidly growing haemangiomas and they can cause significant pain and bleeding.[2] Segmental haemangiomas in the head and neck especially the ophthalmic, maxillary or scalp areas, should alert one to the possibility of PHACE syndrome (Posterior fossa malformations, haemangiomas, arterial anomalies, cardiac and eye abnormalities).[9] Periorbital IH needs special attention as in the reported case 1. The eyelid haemangioma may be responsible for complete visual-axis occlusion or compression of the eyeball and cornea. An emergency intervention is warranted when a haemangioma compromises the airway.[2] Hepatic haemangiomas should be screened for, in babies presenting with large IHs.[1]

The treatment of IH is always individualised to the specific lesion. It is during the phase of proliferation that early treatment is considered if the rate of growth is significant or ulceration and bleeding occur. The non-surgical methods are always preferred during the proliferative phase.[1] Since 1967, systemic corticosteroids were the mainstay in the medical management of IH, following an incidental discovery of the beneficial effects of steroids by Zarem and Edgerton.[1] Propranolol, a non-selective beta-blocker was found to be beneficial on the growth of haemangiomas and have become the first-line of treatment for IHs during the past few years.[10] Leaute-Labreze et al[2] used propranolol to treat hypertrophic obstructive cardiomyopathy, in a young infant with coexisting nasal IH, and the haemangioma regressed rapidly and serendipitously. Most of the reports on propranolol treatment have shown a change in colour from intense red to purple with softening after 24 hours of treatment, as observed in our reported cases as well. Contraindications for the use of propranolol in IH include atopic diseases, bradyarrythmias, episodes of wheezing and hypoglycaemia. Adverse effects of propranolol reported include bradycardia, hypotension, and onset of wheezing, insomnia, agitation and hypoglycaemia.[11] None of the above listed adverse effects were noted in either of the reported cases. The efficacy and safety of propranolol therapy has been highlighted by Schiestl et al in a recent publication.[3] A number of possible explanations to the effects of propranolol have been suggested: localised vasoconstriction; apoptosis of capillary endothelial cells; and the suppressive effects of propranolol on haemangiomas, through the decreased expression of VEGF and bFGF genes.[1,2,10] In 2012, Chim et al[12] have suggested that propranolol exerts its suppressive effects on haemangiomas, through the hypoxia inducible factor (HIF)-1α—VEGF-A angiogenesis axis.

As published in the Cochrane database, there are 8 ongoing trials, 4 of which were designed to assess the effectiveness of oral propranolol; either against placebo or oral corticosteroid.[13] Long-term developmental outcomes of the children, who were treated with propranolol, are warranted because of the high-risk of neuro-developmental delay, following occult hypoglycaemia-induced brain injury.

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