

# A revolution in the management of infantile haemangiomas

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## SUMMARY

In a letter to the editor, Léauté-Labrèze and colleagues describe the chance observation of the significant beneficial effects of propranolol on infantile haemangiomas (IH). A child, aged four months, had a large nasal IH, which had not responded to standard treatment with oral prednisolone (3 mg/kg/day). Coincidentally, the infant developed hypertrophic obstructive cardiomyopathy and was commenced on propranolol, 3 mg/kg/day. Within 24 hours, the IH was observed to be regressing and had completely flattened by 14 months of age.

A second infant, with an extensive IH affecting the entire right upper limb and face, had also not responded to high-dose prednisolone. He developed high cardiac output so was initiated on propranolol, 2 mg/kg/day. Within seven days there was marked improvement in the haemangioma. The systemic steroids were discontinued at four months of age, but the haemangioma continued to improve.

With informed consent, the authors then treated an additional nine infants (11 in total) with severe or disfiguring IHs with propranolol (2–3 mg/kg/day). Within 24 hours, a change in the haemangioma from intense red to purple was apparent in all infants; this change was associated with a palpable softening of the lesions.

A subsequent paper described the results of treating 32 children (21 girls; mean age at onset of treatment: 4.2 months) with large IHs with propranolol.<sup>1</sup> Immediate effects on colour and growth were noted in all cases and were especially dramatic in haemangiomas complicated by dyspnoea, haemodynamic compromise or palpebral occlusion. In ulcerated haemangiomas, complete healing occurred within two months.

## OPINION

Infantile haemangiomas, previously called capillary haemangiomas, are the most common soft-tissue tumours of infancy. They are benign vascular neoplasms with a characteristic clinical course.<sup>2</sup> During the

proliferative phase (birth to 12 months), rapidly dividing endothelial cells are responsible for the enlargement of the IH. This is followed by an involutinal phase, such that most IHs have clinically resolved by age 7–9 years. While it is estimated that 10–12% of children may develop an IH, the majority are small and require no treatment. Unfortunately, a few impair vital or sensory functions, or cause significant permanent disfigurement.

The aetiology of IH remains unclear. A significant advance was the classification of haemangiomas and vascular malformations based on endothelial cell characteristics.<sup>3</sup> It has since been hypothesised that during the third trimester of fetal development, immature endothelial cells coexist with immature pericytes, which maintain their proliferative capacity for a limited period during postnatal life. Angiogenic peptides, including vascular endothelial growth factor (VEGF), beta-fibroblast growth factor (βFGF) and proliferating cell nuclear antigen, may induce proliferation of these immature cells, resulting in the development of the IH. As the endothelial cells differentiate, mast cells migrate into the IH, releasing interferon and transforming growth factor, which terminate this proliferation. Involution of the haemangioma then occurs through senescence of these endothelial cells.

Prior to June 2008, rapidly growing IHs causing functional problems were treated with protracted courses of very high-dose prednisolone (2–5 mg/kg/day, often for 4–8 months), interferon-α or vincristine. Adverse effects often limited their use.

The observation by Léauté-Labrèze and colleagues has been met with great excitement by those who treat IHs, and has already revolutionised the management of this condition. Precise details of the most appropriate dosage, length of treatment and which haemangiomas respond best are still to be clarified. It would be nice to see randomised placebo-controlled studies, but the speed and magnitude of the response of IHs to propranolol may make this difficult. However, there is already a trend to treat smaller, non-complicated IHs, which should be resisted until such studies have been performed.

The mechanism of action of propranolol in IHs is unknown, but it may include simple vasoconstriction, decreased expression of VEGF and  $\beta$ FGF genes through downregulation of the RAF-mitogen-activated protein kinase pathway or triggering of apoptosis of endothelial cells.

It is rare for a single observation to lead to a major paradigm shift in treatment. This one certainly has, and emphasises the value of careful clinical observation.

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