# Propranolol for Infantile Haemangiomas: Experience from a Tertiary Center

**Aim**: Infantile haemangiomas are the most common tumor of infancy. We report the use of propranolol for treatment of problematic and complicated haemangiomas. **Patients and Methods:** Propranolol was given to 52 children with mean age of 18.2 months at onset of treatment. After clinical and electrocardiographic evaluations, propranolol was administered with a starting dose of 2 mg/kg per day, given in 3 divided doses. Monthly follow up was done, response to oral propranolol therapy and any complications of therapy were recorded. Response to propranolol was classified as Complete Response, Excellent Response, Partial Response and Non Responder. **Results:** Total 49 patients showed significant improvement after propranolol therapy out of which 4 patients were complete responder, 30 patients (56.7%) were excellent responders; 15 patients (28.8%) were partial responders. 3 patients (5.7%) had growth of haemangiomas despite propranolol therapy and were classified as non-responder. Side effect like hypotension, rashes, gastroesophageal reflux was reported by 3 patients. In our study mean duration of treatment was 6.5 months. At the end of treatment propranolol was stopped by with gradual tapering of dose over a period of 2 weeks. **Conclusion:** Propranolol administered orally at 2 mg/kg per day has rapid effective therapeutic effect in treatment of ulcerated haemangiomas and it appears to be a valuable and effective treatment option for infantile haemangiomas beyond the proliferative phase, and esthetically disfiguring haemangiomas.

**KEYWORDS:** Adverse effects, infantile haemangiomas, propranolol, ulcerated haemangiomas

## INTRODUCTION

Infantile haemangiomas (IHs) are the most common vascular tumours of infancy.[1] IHs grow rapidly during the first 6-12 months of life (the proliferative phase), enters the second stage of growth proportionate with that of child and then enters a phase of slow regression (involuting phase) lasting 1-7 years.[2] In certain anatomic areas IHs may cause disfigurement or threaten vital functions (such as visual oral or airway function) or may become complicated with painful ulceration and bleeding. These haemangiomas require early and aggressive treatment for ideal functional and cosmetic outcomes.[3] Current treatment option for non-involuted complicated haemangiomas include systemic or intra-lesional corticosteroids, chemotherapeutic agents (vincristine, alpha interferon), laser, surgery or combination of these therapies.[4,5] Propranolol hydrochloride has been recently used for treatment of IHs and appears to have fewer side effects than systemic corticosteroids, can be used for IHs beyond the proliferative phase, and is inexpensive.[6]

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We conducted this study to assess the therapeutic benefit and side effect of propranolol as a treatment option for non-involuted congenital haemangiomas, complicated and problematic infantile haemangiomas, which interfere with normal function and cosmetic development.

## MATERIALS AND METHODS

This prospective study was conducted in the department of Paediatric surgery S.S. Hospital, BHU Varanasi between July 2011 and June 2013. Approval for this study

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was obtained by the institutional ethical committee. All patients up to the age of 12 years with non-involuted congenital haemangiomas, problematic and complicated IHs (proliferative and non-proliferative stage), were included in the study after informed and written consent from parents. Complicated haemangiomas were defined as haemangiomas causing disfigurement, threatening vital functions (such as visual oral or airway function) or complicated with painful ulceration and bleeding. A careful patient history, clinical examination and electrocardiography (ECG) were performed in all the patients to ascertain risk factors or contraindications regarding use of propranolol. Patients with cardiovascular disorder (after cardiac evaluation and ECG), active upper respiratory tract infection and prior history of wheeze were excluded from study. Data were collected about age, sex, location of haemangiomas. Base line haemogram, blood sugar and renal function test were done in all patients. Oral propranolol was given to all patients in a dose of 2 mg/kg body weight in three divided doses as outpatients. Parents were informed about the possible side effects and danger signs like refusal to feed, lethargy and were advised to report at the earliest if any of these signs appeared. Subsequent admission, blood pressure measurement and blood sugar assessment was done in all patients presenting with these danger signs and were managed accordingly. No serial monitoring was done for patients without any side effects or danger signs. Serial monthly photographs were taken during the course of treatment to assess response to oral propranolol therapy for change in size and appearance towards resolution and any complications of therapy were recorded. Response was assessed by treating surgeon and one senior resident. Response to propranolol was classified as *Complete Response* with apparently no residual disease, *Excellent Response* with minimal residual disease, not requiring adjuvant treatment, *Partial Response* with residual disease requiring adjuvant treatment and *Non Responder* with no response or progressive increase in lesion size even after 6 months of treatment.

In patients with proliferating lesions, treatment proceeded from the proliferative phase to the theoretic conclusion of hemangioma growth at 12 months of age. Patients in the involutional phase remained on propranolol for at least 6 months and until resolution or observation of benefit ceases for 1 month. Propranolol was weaned at the end of treatment by gradually reducing the dose to one half over a period of 1–2 weeks. Partial and non-responders to propranolol underwent adjuvant therapy: intra-lesional steroid, intra-lesional bleomycin or surgical excision.

## RESULTS

Over a 24-month period, propranolol was given to 52 cases out of which 48 were IH (43 proliferative and 5 non-proliferative stage) and 6 were of non-involuted congenital haemangiomas. Mean age at therapeutic initiation was 18.3 ± 12.4 months (1 month to 10 years). Head and neck ($n$ = 13) was most common location followed by face ($n$ = 13), trunk ($n$ = 11), extremity ($n$ = 8), intra-oral ($n$ = 5) and genitalia ($n$ = 2). Of these, eight patients had multifocal haemangiomas involving more than one anatomic site. Indications for treatment were ulceration (8), cosmetic (11), functional (15), bleeding (16) and problematic handling (2). Twenty-four (46.15%) patients had rapidly progressing haemangiomas. A total of 25 (48%) patients had received adjuvant treatment with either oral or intra-lesional steroids or intra-lesional bleomycin. Propranolol was started in these patients when complete response to alternate therapies was not evident (mean follow-up, 5.5 months). A total of 49 patients showed significant improvement after propranolol therapy out of which 4 patients were complete responder, 30 patients (56.7%) were excellent responders [Figures 1 and 2]; 15 patients (28.8%) were partial responders [Figures 3 and 4]. Three patients (5.7%) had growth of haemangiomas despite propranolol therapy and were classified as non-responders. Adjuvant therapies used in partial responders were intra-lesional

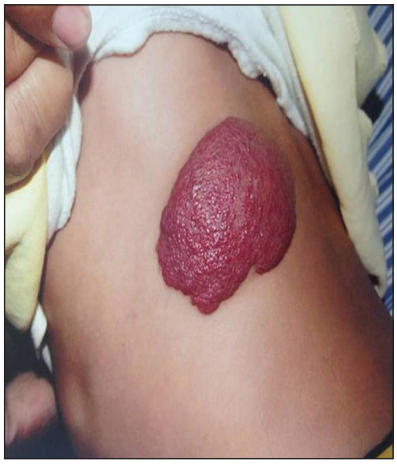

**Figure 1: Pre-treatment photograph of complete responder**

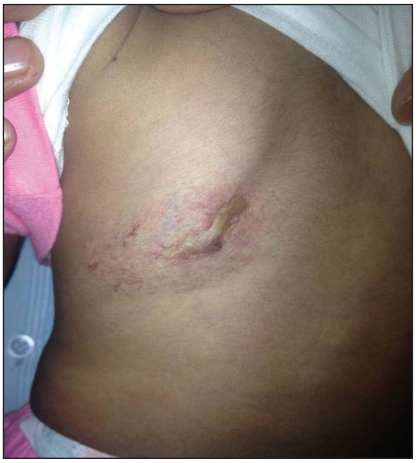

**Figure 2: Post-treatment photograph of complete responder**

steroids ($n$ = 2), intra-lesional bleomycin ($n$ = 4) and surgical excision ($n$ = 9). In non–responders, intra-lesional steroid injections was given in patients with periorbital lesions ($n$ = 1) and intra-lesional bleomycin was given in large bulky lesions ($n$ = 1) and surgery was performed on a large periorbital lesion. In our study we treated eight patients of haemangiomas with ulceration, all were excellent responders [Figures 5 and 6]. The mean duration of treatment was 6.5 ± 3.4 months. Superficial and progressive lesions responded faster compared with lesions with large deeper component and in non-proliferative phase. At the end of treatment propranolol was stopped by gradual tapering of dose over a period of 2 weeks as chronic use may lead to withdrawal symptoms of tachycardia, hypertension, angina, myocardial infarction.[8,14] In one patient presenting with lethargy and refusal to feed, hypotension was recorded at admission. One patient presented with excessive regurgitation (gastrooesophageal reflux) of feeds one week following initiation of treatment. One patient presented with maculo-papular rash involving face and trunk after 2 weeks of initiation of therapy. All these cases responded to withdrawal of drug. There were no reports of serious side effects related to cardiac events, bronchospasm or hypoglycaemia.

## DISCUSSION

IHs are the most common soft-tissue tumours of infancy, occurring in 4–10% of children under 1 year of age, with a clear female predominance (female/male ratio: 4:1).[7] Haemangiomas may not be apparent at birth or may appear as flat circumscribed lesions with telangiectatic vessels on the surface. They enter a phase of rapid growth with superficial and/or deep components, which lasts usually 3–6 months followed by period of stabilisation for a few months and spontaneous involution usually occurs in several years.[8]

About 10% require treatment during the proliferative phase, because of life-threatening locations, local complications, cosmetics or functional risks.[9] We registered 466 new cases of haemangiomas during the study period, out of which 60 (12.8%) required some kind of intervention.

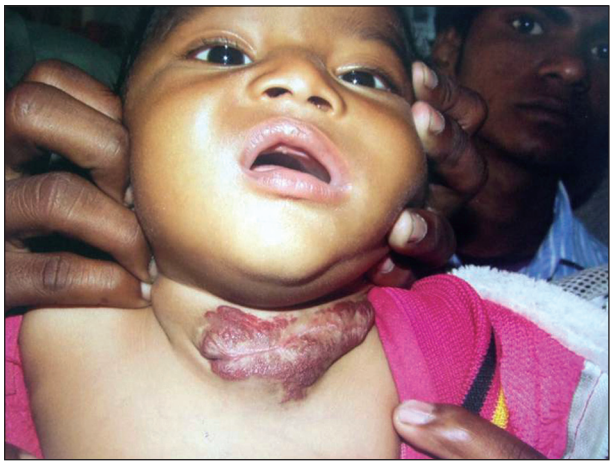

**Figure 3: Pre-treatment photograph of partial responder**

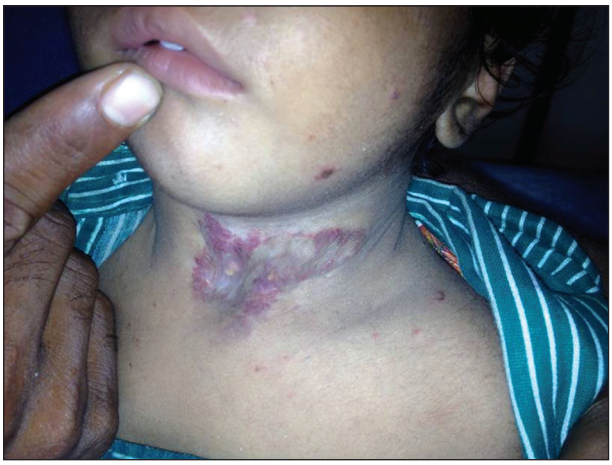

**Figure 4: Post-treatment photograph of partial responder**

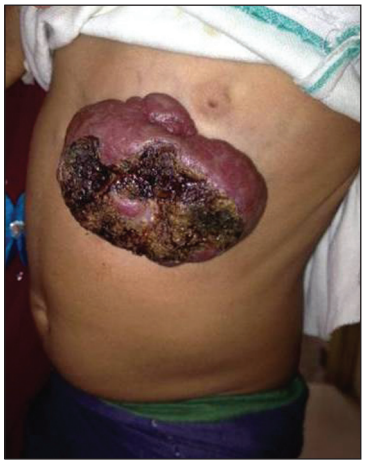

**Figure 5: Pre-treatment photograph of ulcerated haemangioma**

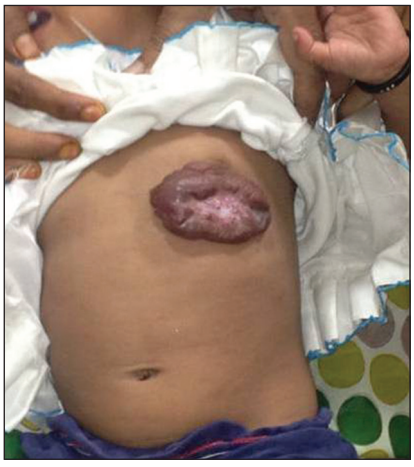

**Figure 6: Post-treatment photograph of ulcerated haemangioma**

The conventional approach in complicated cases is to use systemic corticosteroid therapy as first-line treatment and then interferon or vincristine as second- or third-line therapeutic agents.[10] Propranolol has been found to reduce the size of haemangiomas and lighten the colour during the proliferative phase of development. Beta adrenergic receptors are present on endothelial cells. Mechanisms, such as vasoconstriction, endothelial cell apoptosis and decreased angiogenesis, have been proposed to explain how propranolol affects IHs, although exact mechanism remains unclear.[11] Beta blockers inhibit vasodilatation, which leads to immediate changes in the IHs, due to decreased blood flow from the capillaries feeding the IH and can be observed as colour lightening and softening within the first 3 days of initiating treatment.[12] Angiogenic growth factors are important in endothelial cell proliferation. Beta blockers are proposed to down-regulate angiogenic growth factors, such as vascular endothelial growth factor (VEGF-A), matrix metalloproteinases (MMP-2 and MMP-9) and interleukin 6 (IL-6).[13]

The pharmacologically optimal dosing interval for propranolol is every 6 hours, but compliance is better if the medication is given every 8-12 hours.[17] We gave propranolol in dose of 2 mg/kg given at 8-hour interval as utilised in most patients by Leaute-Labreze *et al*.[11] For infants less than 3 months of age, starting dose was 1 mg/kg escalated to 2 mg/kg over period of 1 week.[17] We treated our patients as outpatients. Parents were informed about the possible side effects and danger signs like refusal to feed, lethargy and advised to report at the earliest if any of these signs appear. Buckmiller *et al*., treated 41 cases with 39% excellent responders, 36% partial responder and 2.5% were non-responder.[18] Similarly Qin *et al*. conducted therapy in 58 patients; out of which, 17% were excellent responders, 60% had good response, 20% had moderate response and 1.7% were non-responders.[19] We had similar results with 7.6% patients complete responders, 56.7% excellent responders, 28.8% partial responders and 5.7% were non-responders. The reason for this variable response is not clear, although reports have suggested that it is due to variability in tumour composition. The control of the deep elements is more critical to functional and cosmetic sequelae, as this reduces the need of surgical intervention.[18]

The most common complication of IHs is ulceration, in up to 15-25% of IHs.[16,20] Treatment modalities like topical, intra-lesional or systemic steroids are contraindicated in such cases because most of these cases are associated with secondary infection. In our study we treated eight patients of haemangiomas with ulceration, all were excellent responders. All showed improvement in size and pain within 1 week of initiation of treatment. Similar results have been shown by Saint-Jean *et al*., on 33 infants with problematic ulcerated haemangiomas in a retrospective review.[21]

At the end of treatment propranolol was stopped by gradual tapering of dose over a period of 2 weeks, as abrupt discontinuation causes ventricular arrhythmias.[8,22] Three of our patients with excellent response had relapse with increase in the size of lesion within a month of completion of therapy. In one patient with relapse, rapid progressive nature of relapse required restart of propranolol therapy, in other two cases lesions stabilised over 2-4 weeks. Similarly other studies have shown relapse after propranolol is stopped, although rates and magnitude of relapse varies.[10,15]

In our study, three patients had side effects out of which one patient had hypotension, one had gastro-oesophageal reflux and one patient complained of rashes. There were no reports of serious side effects related to cardiac events, bronchospasm or hypoglycaemia. All responded to conservative treatment.

## CONCLUSION

Propranolol is a valuable therapeutic alternative for treatment of ulcerated haemangiomas where modalities like glucocorticoid can be detrimental with increased chances of infection with their use. Propranolol is an effective treatment option for non-involuted congenital haemangiomas and IHs even beyond the proliferative phase, and esthetically disfiguring haemangiomas. At therapeutic doses, propranolol is safe and effective in the majority of patients. Long-term follow-up remains paramount for understanding and accepting propranolol as a potential first-line treatment for haemangiomas. Variability in response also suggests the possibility of variability in tumour composition in haemangiomas. Nonetheless, this study supports the use of propranolol in IHs beyond the proliferative phase, complicated and esthetically disfiguring haemangiomas especially ulcerated haemangiomas. Propranolol is likely to revolutionise the management of haemangiomas, although consensus guidelines are required regarding optimal dose, duration, patient selection criteria and safety profile.

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