ORIGINAL ARTICLE

# Use of propranolol in infantile haemangioma among Chinese children

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**Objective** To describe the use of propranolol as first-line treatment or as single therapy to control the proliferating phase of infantile haemangioma in Chinese children.

**Design** Retrospective study.

**Setting** Regional hospital, Hong Kong.

**Patients** Children 3 years old or younger with facial haemangioma who took oral propranolol between 1 December 2008 and 1 December 2009.

**Results** There were 12 such patients, all of whom underwent prior clinical evaluation before starting the treatment. Ten patients had a solitary facial haemangioma and two had multiple haemangiomas. The mean age of symptom onset was 12 days. The mean age for starting propranolol treatment was 7 months, and in all cases a clinical response was observed within 7 days. Five (41%) of the patients had complete resolution 2 to 6 months after starting medication, at which time they were 5 to 12 months old. Two of them had a recurrence of the haemangioma within 8 weeks of stopping the drug, but responded to a second treatment course. In these two patients, the propranolol dosage had been tailed down rapidly and the therapy was of a shorter duration than in those without recurrence. The remaining seven patients are still taking propranolol and responding satisfactorily. Hypotension was observed in two patients, one of whom tolerated a lower dose and in the other, therapy was reinitiated at her older age. No serious side-effect was encountered in the remaining patients.

**Conclusion** Propranolol was useful as first-line or single-agent treatment of facial infantile haemangioma in Chinese children, and gave rise to minimal side-effects. Although recurrence of infantile haemangioma occurred after propranolol was tailed off rapidly after a relatively short duration, an optimal treatment duration and tapering schedule has not yet been defined. Nevertheless, patients responded well to second courses of propranolol therapy.

## Introduction

Infantile haemangioma (IH) is a common vascular birth-mark. The prevalence of IH is approximately 1 to 3% after the first few days of life and approximately 10% by the end of the first year. We frequently encounter such children in our paediatric skin clinic. In most of them, lesions run a benign course and resolve spontaneously. In some patients however, they ulcerate and the superficial components bleed, especially in those whose haemangiomas are located over frictional areas such as the lip or perineum. This may adversely affect the eating habits of these children and how they are cleansed. After spontaneous resolution they could also be left with permanent scars, redundant fibro-fatty tissue and telangiectases. Large facial haemangiomas—those located at the nose, lip, ear, glabellar area, and those with prominent deep components—are prone to give rise to disfiguration as they resolve.[1] Those located around orificial areas, such as an eye or nostril, could even give rise to amblyopia or airway obstruction. Very rarely, they may cause severe thrombocytopenia or coagulopathy that results from platelet trapping within the vascular tumour (Kasabach-Merritt syndrome), or congestive heart failure. Besides potential medical problems, an IH may impose significant psychological distress on the family and the patient.

Treatment of IH can be conservative unless it obstructs a vital passage or causes any life-threatening complication. In complicated cases, such as persons at risk of obstructing

**Key words**
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## 用普荼洛爾治療華籍嬰兒性毛細血管瘤患者

**目的** 描述利用普荼洛爾（propranolol）作一綫治療或單一治療來控制嬰兒性毛細血管瘤的增殖期。

**設計** 回顧研究。

**安排** 香港一所分區醫院。

**患者** 2008年12月1日至2009年12月1日期間，有面部血管瘤而服用普荼洛爾的3歲或以下的兒童。

**結果** 共12名患有毛細血管瘤的兒童經臨床檢查後開始服用普荼洛爾。其中10名有孤立性面部血管瘤，另2名有多發性血管瘤。病人出現症狀的平均年齡為12天，而開始治療的平均年齡為7個月，所有病人均於服用普荼洛爾7天內有臨床反應。5名（41%）由5至12個月大的病人於開始治療的2至6個月後完全康復；其中有2名病人停藥後8個星期內有復發，他們都對再次服藥有反應；與其他沒有復發的病人比較，這2名病人服藥的時間較短，劑量亦調低得快。其餘7名病人繼續服用普荼洛爾，並有滿意效果。有2名病人出現低血壓，其中一名被調低用藥劑量後繼續接受治療，另一名則於年紀較大的時候再次服藥。其餘病人均沒有不良反應。

**結論** 用普荼洛爾作一綫治療或單一治療嬰兒性面部毛細血管瘤有效，副作用亦很少。雖然服藥時間較短及調低用藥劑量可能會出現復發，目前尚未有最佳治療期及劑量的參考資料。無論如何，對於復發的病人，再次施以普荼洛爾都可成功治療此症。


the visual axis or airway, or those associated with high-output heart failure, intralesional or systemic corticosteroids have been used. For persons with haemangiomas with life-threatening complications, interferon alfa-2a[2] or vincristine[3,4] have also been given. All of the above treatments, however, may give rise to significant side-effects. In recent years, Léauté-Labrèze et al[5] observed that propranolol can inhibit the growth of IH lesions in children. This finding was further supported by Sans et al's study,[6] which concluded that oral propranolol had a consistent and rapid therapeutic effect on IH. However, according to our information, the benefits of propranolol therapy have not been reported in Chinese children with IH. Thus, this is the first study of propranolol treatment in Chinese children with facial haemangioma.

## Methods

### Sample selection

We searched the Clinical Data Analysis and Reporting System using diagnostic codes 228.00 and 228.01 (haemangioma/facial haemangioma) of the International Classification of Diseases, 9th revision, Clinical Modification AND discharge date between 1 December 2008 and 1 December 2009 AND age of 3 years or younger AND with a prescription for 'propranolol'. A patient name list was generated, and every patient's medical record was traced and comprehensively reviewed from admission to discharge.

### Data collection

Demographic and clinical data included: each patient's gender, gestational age, the age when the lesion first

TABLE. Demographic data of the 12 children having an infantile haemangioma (IH)

| Patient No. | Sex | Gestational age (weeks) | Age when lesion first appeared (days) | Location of IH | Indication for treatment | Treatment with corticosteroids |
|---|---|---|---|---|---|---|
| 1 | F | FT* | 28 | Left temporal | Dis-figure | No |
| 2 | F | FT | 21 | Lower lip | Functional risk | No |
| 3 | F | FT | 7 | Left temporal | Dis-figure | No |
| 4 | F | FT | 7 | Left periorbital | Functional risk | No |
| 5 | M | 36 | 14 | Left temporal | Dis-figure | No |
| 6 | F | 36 | 7 | Multiple, lower lip and tongue | Functional risk | No |
| 7 | F | 23 | 7 | Left temporal | Dis-figure | No |
| 8 | F | 36 | 14 | Right periorbital | Functional risk | Yes† |
| 9 | F | FT | 7 | Lower lip | Functional risk | Yes‡ |
| 10 | F | FT | 14 | Right cheek extend to parotid and ear back | Dis-figure | Yes§ |
| 11 | M | 34 | 14 | Multiple, right ala nasi, chest and spine | Dis-figure | No |
| 12 | F | FT | 14 | Left cheek | Dis-figure | No |

* FT denotes full-term
† Prednisone, 2 mg/kg/day, was given at 1 and 2 months old, followed by one intralesional steroid injection
‡ Prednisone, 2 mg/kg/day, at 3 months old, intussusception after 13 days of treatment requiring surgical intervention. Oral prednisolone was stopped; propranolol was reinitiated at the age of 8 months
§ Intralesional steroid injection twice at 6 and 7 months old in China
¶ This patient was first seen at 19 months in our specialty clinic

appeared, location of the lesion, treatment indications, previous corticosteroid and adjunctive laser treatment. In addition, details regarding propranolol treatment, including the dosage, and age when first started and terminated, were obtained from the medical records, reviewed, and analysed. For comparison, clinical photos were taken before, during, and after treatment.

### Treatment protocol

Patients 3 years old or younger and with facial haemangioma obstructing the vital organs, causing disfigurement, or having mixed or deep haemangiomas over exposed areas were considered for propranolol treatment.[1] Absolute and relative contra-indication to propranolol treatment were asthma, diabetes mellitus, hypoglycaemia, pre-existing bradycardia, sick sinus syndrome, atrioventricular block (second- or third-degree), severe hypotension, uncontrolled congestive heart failure, allergy to propranolol, and according to the package insert, hyperthyroidism and myasthenia. Verbal informed consent was obtained from the parents by the respective paediatricians. The patients were admitted into hospital for baseline assessments, which included: electrocardiography, blood pressure, and capillary blood glucose monitoring. Oral propranolol was given at a starting dose of 0.5 mg/kg per day in three divided doses. During the hospital stays of the patients, blood pressures were monitored before the drug was given and hourly for 3 hours after starting treatment. Oral propranolol was omitted if the child's blood pressure was less than 5th centile according to the age and sex, and resumed if the blood pressure had normalised. The capillary blood glucose was monitored every day. For those with persistent hypotension after taking propranolol, an alternative treatment modality was offered. For patients who tolerated the drug, the dosage was stepped up gradually to 1 mg/kg/day 24 hours as the first dose, then to 2 mg/kg/day at 48 hours so long as there was no bradycardia, hypotension, or hypoglycaemia. Patients were discharged after 72 hours on their final dosage of propranolol, and the treatment continued at home. The patients were re-evaluated in our paediatric dermatology clinic after 7 days, and then every 4 to 6 weeks. Blood pressure, heart rate, treatment compliance, adjustment of dosages according to body weight, and clinical photographic evaluations were performed during each consultation. For patients with peri-orbital IH, ophthalmologists were consulted.

### Outcome measures

Clinical photos were taken before starting propranolol, during out-patient clinic consultations, and after completing the treatment course. Changes in size and colour of the haemangioma were documented by clinical photos. Physical examination of the patients entailed documenting the size and softening in texture of the lesions by any one of three paediatricians with dermatology training.

## Results

Twelve patients with complicated IHs were identified. Demographic data for these children are summarised in the Table. The mean age of symptom onset was

| Age at initiation of propranolol treatment (months) | Propranolol dosage (mg/kg/day) | Duration of propranolol treatment (months) | Clinical outcome |
|---|---|---|---|
| 2 | 2 | 3 | Complete response |
| 3 | 1 | 6 | Complete response, with adjunctive laser therapy |
| 2<br>6 (2nd course) | 2 | 2<br>4 (2nd course) | Relapse after 1st treatment course; complete response after 2nd treatment course |
| 4 | 2 | 3 | Complete response |
| 4 | 2 | 5 (ongoing) | Partial response |
| 9 | 2 | 4 (ongoing) | Partial response |
| 22[¶] | 2 | 5 (ongoing) | Partial response |
| 12 | 2 | 4 (ongoing) | Partial response |
| 2 | 2 | 4 (ongoing) | Partial response with adjunctive laser therapy |
| 8 | 2 | 5 (ongoing) | Partial response with adjunctive laser therapy |
| 2 | 2 | 5 (ongoing) | Partial response with adjunctive laser therapy |
| 11<br>15 (2nd course) | 2 | 2<br>5 (ongoing) | Relapse after 1st treatment course; partial response to 2nd treatment course |

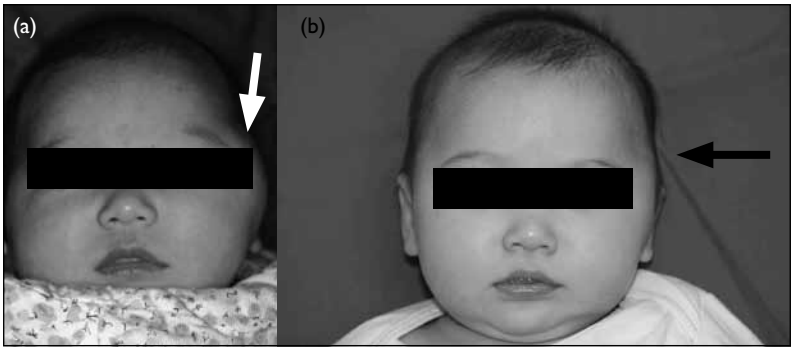


FIG 1. Patient No. 1: (a) pretreatment and (b) 4 weeks after discontinuing the 3-month treatment course, with infantile haemangioma shown (arrows)

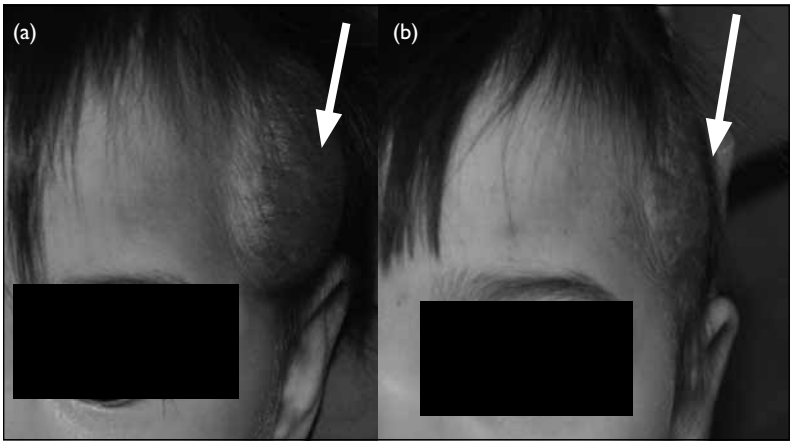


FIG 2. Patient No. 7: (a) pretreatment and (b) after 8 weeks of propranolol treatment, with infantile haemangioma shown (arrows)

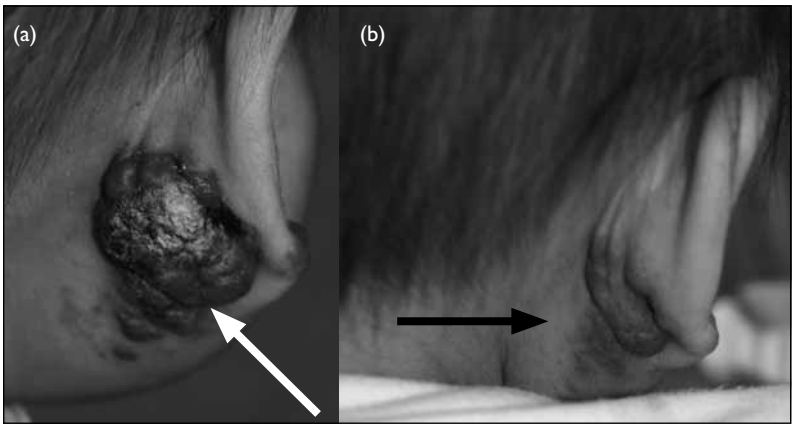


FIG 3. Patient No. 10: (a) pretreatment photo showing a large ulcerated infantile haemangioma (arrow) over posterior ear lob and involving the right face, and (b) 4 months after propranolol treatment with adjunctive laser treatment, showing infantile haemangioma (arrow) over posterior ear lobe healed with telangiectases

on day 12 (range, 7-28 days). Among them, 10 had solitary facial haemangioma, located around the temporal region (33%), lower lip (17%), cheek (17%), and periorbital area (17%). The remaining two babies had multiple haemangiomas, one on the lower lip and tongue and another over the ala nasi, upper chest, and lower sacral spine. Eight (67%) babies had mixed superficial and deep components to their haemangiomas; two had superficial haemangiomas, and two others had deep haemangiomas. All of the babies fulfilled the treatment criteria of the American Academy of Dermatology Guidelines/Outcomes Committee.[1] The Committee suggested that patients with life- and function-threatening haemangiomas, large facial haemangiomas, haemangiomas located at the nose, lip, ear, and glabellar area, haemangiomas with a prominent dermal components or that were pedunculated had an indication for treatment. None of our patients had medical contra-indications for the use of propranolol.

After clinical assessment, oral propranolol was given as first-line therapy to 10 babies. Two babies had received other treatment modalities before initiation of propranolol. One had received oral prednisolone in the first and second month of life, followed by intralesional steroid injections, but without any obvious clinical improvement. The other received intralesional steroid injections in China, and according to the mother there was no improvement. Four patients had ulcerations affecting the superficial components of their haemangiomas; they received one to two pulse dye laser (Candela V beam 595 nm) treatments as adjunctive therapy to possibly hasten ulcer healing whilst taking oral propranolol.

The mean age for starting propranolol treatment was 7 (standard deviation, 6; range, 2-22) months; shrinkage in size, softening in consistency, and decrease in redness was evident in all patients within 7 days. Among them, five patients receiving first-line oral propranolol treatment responded within 2 to 6 months. Complete resolution occurred between the ages of 5 and 12 months, for which reason the treatment was discontinued (Figs 1 to 3). Among these five patients, two had recurrences within 8 weeks of ceasing treatment. Patient 3 (Table) started taking propranolol at the age of 2 months and stopped after satisfactory clinical improvement when she was 4 months old. Four weeks later, the haemangioma increased in thickness and redness. At the age of 6 months, propranolol was restarted and continued for 4 months by which time the lesion had completely resolved, and there was no further recurrence. Patient 12 (Table) received 2 months of propranolol treatment at the age of 11 months. Treatment was discontinued when she was 13 months old as the lesion had flattened, softened, and its redness had diminished. Four weeks later the haemangioma had increased in thickness and its redness had increased, for which a second course of propranolol therapy was started and the lesion resolved. These two patients with recurrences and the three others appeared to show good responses to first course of propranolol treatment. Those who endured recurrences had

their propranolol tailed off over 7 days, while in the others the tail-off periods ranging from 4 to 8 weeks. Moreover, treatment duration in the former was 2 months, while in the latter it was 3 to 6 months. The remaining seven children are still taking the propranolol for their haemangiomas, which continue to decrease in size. Regarding the two patients with multiple haemangiomas, including at sites other than the face, these lesions also appeared to be responding well to propranolol treatment.

Regarding the side-effects of treatment, while taking low-dose propranolol (1 mg/kg/day) a 3-month-old patient had asymptomatic hypotension (systolic blood pressure persistently below 5th centile), which was detected during routine checking of the blood pressure. Her blood pressure persisted around the 5th centile despite adjustment of the dose to 0.8 mg/kg/day. Propranolol treatment was then withheld and prednisolone substituted for 1 week. Her haemangioma proliferated rapidly, bled, and ulcerated. Propranolol treatment was cautiously reinitiated at the age of 8 months, and she continues to tolerate this treatment (2 mg/kg/day) well, with ongoing clinical improvement and no complications. Another patient, who received 2 mg/kg/day of propranolol, developed transient asymptomatic hypotension (borderline-low blood pressure at around 5th centile), and was switched to 1 mg/kg/day. One patient manifested wheezing, which was treated by a course of salbutamol inhalations. Propranolol was withheld for 4 months lest it induced bronchospasm and/or made the wheeze worse. When restarted later, there were no complications. All other patients received propranolol 2 mg/kg/day without any adverse effects.

## Discussion

Currently, systemic or intralesional steroids are the mainstay of treatment for complicated IHs, which has been well documented in literature.[1,7,8] The regimen consists of using 2 to 4 mg/kg/day of prednisolone in a single morning dose. The treatment duration (in terms of months) depended on the clinical response.[1] Whilst steroids were effective, the children were liable to complications, including: gastric upset, Cushing's syndrome, and growth retardation.[9] For periorbital lesions, intralesional steroid (triamcinolone acetonide, 10-40 mg/mL[1]) injection was given, but could cause central retinal artery occlusion and even eyelid necrosis.[10,11]

This is the first study in Chinese children demonstrating the efficacy of treating complicated facial IH with propranolol as first-line treatment. The proposed mechanism for the action of propranolol is that it induces vasoconstriction and capillary endothelial cell apoptosis.[12] It also interferes with proangiogenic mechanisms involved in the growth phase of IHs (generation of vascular endothelial and basic fibroblastic growth factors).[6] Sans et al's study[6] recruited 32 patients, among whom around 30% had multiple haemangiomas, which all responded well. This was consistent with the results in our patients with haemangiomas located at sites other than face. In Chang et al's study,[13] complete resolution of the haemangiomas lasted a variable number of years, while deep haemangiomas tended to enter an involuting phase later than superficial lesions. Metry[14] also mentioned that the natural history for haemangiomas was to involute completely within 9 years; the estimated rate of involution being around 10% per year. Therefore around 50% of them would have regressed by the age of 5 years, 70% by 7 years, and 90% by 9 years. In our study, patients achieved complete resolution as early as the age of 5 months, meaning that the cosmetic improvement was attained before the child went to kindergarten, and psychological distress for the child and family could be avoided.

Two of our patients with recurrence of haemangiomas received relatively shorter courses of treatment (2 months as opposed to 3-6 months) and with relatively rapid tail-off therapy. The effect of treatment duration and tail down on haemangioma recurrence was not known and has not been studied. In Sans et al's study,[6] the shortest treatment duration was 2 months in a child who had a mild re-growth. The mean duration of therapy in their study was 6 (range, 2-10) months. Siegfried et al[15] suggested that propranolol should be gradually tapered over a period of 2 weeks. A further study on treatment duration and tail down appears necessary. In the absence of more evidence, we suggest 4 to 6 months of treatment depending on the clinical response, and that the tail down should be gradual over 4 weeks (around 25% every week) and backed up by close monitoring.

Compared with conventional steroid treatment for IH, propranolol was well tolerated and without significant side-effects. Moreover, it has been used in children with supra-ventricular arrhythmias, hypertension and for migraine prophylaxis. Regular monitoring revealed that it was well tolerated and safe. Whereas high-dose systemic steroids cause significant adverse effects, and such children also need to postpone live vaccination schedules. Use of propranolol as first-line treatment for IH can circumvent resorting to high-dose steroids as well as intralesional steroid injections in the periorbital area (which poses a risk of blindness). In our study, only two (17%) patients had transient asymptomatic hypotension while taking the propranolol, one of whom tolerated the drug well when it was reintroduced later and the other tolerated a lower dose; both enjoyed clinical improvement. This suggests that in children who develop side-effects,

temporarily withholding propranolol or a dosage reduction may be appropriate.

## Conclusions

Oral propranolol was useful in treating IH on the face and other body sites among Chinese children. It appeared to hasten the resolution of haemangiomas, was well tolerated, and had minimal side-effects. Recurrence of IH may occur if propranolol is withdrawn after a relatively short course of treatment and/or tailed off rapidly. Recurrence of IH appeared to respond to a second course of treatment.

## Declaration

No conflicts of interest were declared by the authors.

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