

# Propranolol in infantile haemangioma: simplifying pretreatment monitoring

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## Summary

**BACKGROUND:** Infantile haemangiomas (IHs) are very common vascular tumours. Propranolol is at present the first-line treatment for problematic and complicated haemangioma. In accordance with a Swiss protocol, children are monitored for 2 days at the start of the treatment to detect possible side effects of this drug. Our study advocates a simplification of the pretreatment monitoring process.

**METHODS:** All children with a problematic and complicated haemangioma treated with propranolol between September 2009 and September 2012 were included in the study. All patients were hospitalised under constant nurse supervision for 48 hours at the start of the treatment and subjected to cardiac and blood measurements. The dosage of propranolol was 1 mg/kg/day on the first day and 2 mg/kg/day from the second day. Demographic data, clinical features, treatment outcome and complications were analysed.

**RESULTS:** Twenty-nine infants were included in our study. Of these, 86.2% responded immediately to the treatment. There were no severe adverse reactions. Six patients presented transient side effects such as bradycardia, hypotension after the first dose and hypoglycaemia later. No side effects occurred after the second dose. Treatment was never interrupted.

**CONCLUSION:** Propranolol (a  $\beta$ -blocker) is a safe treatment for problematic IH. Side effects may occur after the first dose. A strict 48 hour monitoring in hospital is expensive and may be unnecessary as long as the contraindications for the drug are respected.

**Key words:** *infantile haemangioma; propranolol; vascular tumour*

## Background

Infantile haemangiomas (IHs) are present in 10% of children under the age of 1 year, and are the most common benign tumours of infancy [1]. An especially high incidence of haemangioma has been reported in very premature babies [2, 3]. Eighty percent are solitary lesions. Sixty percent are located in the cervicofacial region, the others arising on the trunk and the extremities. Multiple haemangiomas

(more than five) are known to be associated with visceral lesions, most often hepatic and gastrointestinal [4].

Haemangiomas are proliferative vascular lesions due to an accelerated turnover of endothelial cells. Their appearance within a few weeks after birth is followed by a period of rapid growth during early infancy. The maximum peak of activity occurs between 5 and 6 months of age, and its maximum duration is 1 year [5]. This phase is followed by a stable period of a few months and then a spontaneous involution over several years. During the involution phase, the turgescence of the tumour will decrease and the colour will change from purple-red to grey. The involution may be complete or partial, and the residual skin may be redundant, atrophic and telangiectatic. If spontaneous involution is very rapid, bleeding and ulceration of the tumour may call for surgical excision or laser treatment. Congenital haemangiomas, distinct from the haemangiomas that appear after birth, are tumours which are fully developed at birth, do not have a proliferation phase and regress a few months after birth [3].

As a result of variations in their size, shape and behaviour, infantile haemangioma present a broad spectrum of clinical features and vary greatly in their response to treatment. The choice of treatment of the lesions is determined by their location and rate of growth. Facial, anal, vulvar or mammary haemangiomas may give rise to functional impairment or ulceration [1, 2]. Periorbital haemangiomas may cause visual impairment with amblyopia or anisometropia. Heavy facial haemangiomas may cause lip or eyelid deformation with ectropion. Parotid gland haemangiomas may cause obstruction of the external auditory canal. Anal and vulvar haemangiomas may develop ulceration by irritation. Subglottic lesions may cause stridor and life-threatening airway obstruction. The clinical heterogeneity of these lesions challenges care providers, who have to distinguish among the range of lesions that must be treated rapidly and carefully during early infancy.

Our approach to the treatment of subglottic or infiltrative haemangiomas has been totally modified in view of the remarkable effectiveness of oral propranolol (a  $\beta$ -blocker) [6–8]. Its possible side effects are bradycardia, hypotension and impaired response to hypoglycaemia [9, 10]. The treatment starts with 1 mg/kg/day orally on the first day, raised to 2 mg/kg/day from the second day on. The ideal duration

of treatment and the risk of reappearance of the lesions at the end of the treatment are still subjects of debate [11, 12]. Whereas the efficacy of the treatment with propranolol in stopping the development of proliferative haemangioma is generally recognised, the initial monitoring of the treatment is still a matter of debate. The custom in our country is to hospitalise the children for 48 hours for preliminary blood glucose measurement and cardiac ultrasound investigation, and for monitoring of vital signs at the start of the treatment [13]. The purpose of this study is to point out that the low frequency and severity of drug-related side effects during the initial phase of treatment may justify a simplification of the 48-hour monitoring in a hospital setting.

## Methods

In this retrospective study, we reviewed data from all children with a problematic and complicated haemangioma treated with propranolol between September 2009 and September 2012 in the Paediatric Surgery Department of the University Hospital in Lausanne (CHUV). All the children were treated in accordance with the Swiss protocol established by the Swiss Grand Round for Vascular Anomalies in Childhood [10, 13]. This protocol established the indications for using propranolol in the treatment of problematic haemangiomas (voluminous, multiple, ulcerated) and complicated haemangiomas (face, orifices, extremities, genital or subglottic). Before the initiation of propranolol treatment, blood glucose levels and renal function were first checked, and a cardiac ultrasound and electrocardiogram (ECG) were performed by paediatric cardiologists. Then, when all results were normal, and the parent's consent obtained, patients were hospitalised in our department for continuous monitoring during 48 hours at the start of the treatment. Blood pressure and cardiac rhythm were checked every 30 minutes for 4 hours after the treatment. The treatment with propranolol was initiated with 1 mg/kg/day in the first 24 hours and then 2 mg/kg/day from the second day onwards if the first dose was well tolerated [10, 13]. The dosage was not adapted according to bodyweight from 11 months to the first birthday. Treatment with 2 mg/kg/day propranolol was generally maintained during the first year of life (or longer in the case of recurrence). Heart malformations, respiratory problems such as bronchiolitis or asthma were contraindications to commencing treatment.

For ulcerated haemangiomas, alginate or hydrocolloids dressings with eosin® 2% was used for local treatment in addition to propranolol. After 48 hours, the treatment was continued on an outpatient basis, with oral propranolol 2 mg/kg/day given in three doses. Parents were advised to temporarily discontinue the treatment if problems occurred, especially in cases of bronchiolitis or respiratory problems. Follow-up was organised in our clinic after 1 week and again after 4 weeks and then every 8 weeks. Parents were invited to call in the event of recurrence of the haemangioma. Clinical condition, weight, heart rate and blood pressure were recorded at each visit and dosage of propranolol adapted according to bodyweight. Characteristics of the haemangioma, such as colour, size and consistency were evaluated. Photographs were taken as an objective

tool of comparison. Possible treatment complications were noted.

Treatment evaluation, based on clinical examination and photographs, was performed by the same team of surgeons experienced in treating haemangiomas and vascular malformations. Epidemiological data, IH clinical features, treatment outcome and complications were collected from medical files.

Response to propranolol was categorised as excellent, moderate or absent. Excellent response was defined as a rapid initial discoloration and noticeable decrease in the size of the tumour. Clinical response was considered good when spontaneous ocular opening and healing of ulceration with relief from pain were observed. The response was qualified as moderate when improvement was less obviously present.

## Results

Twenty-nine patients were treated with propranolol between September 2009 and September 2012. There was a predominance of female patients (21/8). Five patients were preterm.

Twenty patients (67%) had a solitary haemangioma and nine had multiple ones. Haemangioma were located respectively on the face (fig. 1), on the trunk, on the extremities, in the subglottic areas, and in the genital areas (table 1 and fig. 2). Twenty-two children had a cutaneous tumour, nine had a subcutaneous tumour and seven deep haemangioma. Deep ulceration was observed in four children on their first clinical examination. Prior to the initiation of pro-



**Figure 1**

Infantile haemangioma of the face at 2 months (left) and after 2 weeks (right) of treatment with propranolol (2 mg/kg/day).



**Figure 2**

Two examples of genital area haemangiomas complicated by ulceration. Left: before treatment. Right: after treatment with propranolol (2 mg/kg/day).

pranolol treatment, all cardiac ultrasound and ECGs performed by paediatric cardiologists were normal, and all children could start the treatment. None of the children had respiratory problems, with bronchiolitis or asthma postponing the treatment. Blood glucose levels and renal function were all normal and consent was obtained from all parents after our explanation.

Eleven patients underwent diagnostic imaging or endoscopic studies: three endoscopies for respiratory tract obstruction, three magnetic resonance imaging (MRI) examinations for subcutaneous orbital tumours, three ultrasound examinations for parotid mass, and two abdominal ultrasound examinations because of multiple cutaneous haemangiomas (>5) without an associated visceral tumour. Clinical examination alone was sufficient to reach a diagnosis in the remaining cases. Four patients (13.8%) had previously received treatment for their haemangioma: two were already being treated with a corticosteroid, without any positive response, and three had been treated with pulsed-dye laser.

The median age at the start of propranolol treatment was 3.5 months, ranging from 1.5 to 12 months. Propranolol was started at 1mg/kg/day in all patients. The initial response to the drug was excellent in 25 out of 29 children (86.2%) and moderate in four.

The median duration of the treatment was 7.1 months (range: 4 to 16 months) for 28 children. One patient, who is now 3 years old, is still under treatment because of the immediate recurrence of the haemangioma when we tried to stop the treatment. Three patients were still being treated after 1 year of age because we observed a rebound of the lesions when the treatment was stopped. The treatment was continued after their first birthday for 3 (twice) and 4 months. No late recurrence of a haemangioma was noted in our study.

None of our patients showed severe side effects at the beginning or during the treatment. We did, however, have four mild cases of transient decreased blood pressure (a decrease of more than 15% of mean arterial pressure): the children's ages were 7 months and 20 days, 7 months and 10 days, 9 months and 6 days, and 11 months (table 2). These children were not the youngest among our population. For two of them, we remained at a dosage of 1mg/

kg/day because even with this lower dosage, the effectiveness on the haemangioma was excellent. Two other children presented a lower heart rate after the first dose of the drug. No other clinical symptoms were noticed and the dose was increased to 2 mg/kg/day. One child had late hypoglycaemia at 7 months after 3 months of treatment.

## Discussion

As haemangiomas will spontaneously decrease after a few years, treatment during the proliferation phase is reserved for functional or psychological problems, or bleeding and ulceration of the tumour if spontaneous involution is very rapid. Depending on the rhythm of proliferation, ulceration and bleeding, as well as congestive heart failure, may occur. However, there are no indicators to predict the eventual volume of a particular haemangioma or forecast the timing and outcome of evolution or involution.

During the proliferation phase, the endothelial cells are tightly packed sinusoidal channels with multilaminated basement membrane and numerous cellular mitoses [14]. During the involution phase, the lesion presents a decrease of endothelial proliferation, a decrease in cellularity and size, large vascular channels, apoptosis and fat proliferation with fibrous septa and softness of the overlying skin. The type of involution cannot be predicted; it may be complete or partial, and the residual skin could be redundant, atrophic and telangiectatic.

Oral steroids are, if possible, no longer given, because of side effects such as Cushing's syndrome, with growth retardation, hirsutism, arterial hypertension, immunosuppression and increased risks of infection [5]. Interferon therapy for subglottic haemangiomas induces the involution of the tumour through endothelial cell apoptosis, but also causes side effects such as malaise, spastic diplegia, neutropenia and liver enzymes increases [16]. Carbon dioxide laser ablation, also used for subglottic haemangiomas, induces scarring and laryngeal stenosis, which could require a tracheostomy. Direct injection of steroids (beta-methasone) requires general anaesthesia and has been associated with necrosis, skin atrophy or globe penetration. Chemotherapy and radiation have side effects such as peri-

**Table 1:** Location of 40 haemangiomas in 29 children.

	Number	%
Face	21	52
Trunk	6	15
Extremities	7	18
Subglottic area	3	7.5
Genital area	3	7.5

**Table 2:** Summary of the adverse effects of propranolol treatment.

Patient	Gender	Age at the beginning of treatment	Adverse effect	When		Location of tumour
				Early	Late	
8	F	4 mo 21 d	Bradycardia	First dose		Subglottic
11	F	7 mo 20 d	Hypotension	First dose		Face
15	F	7 mo 10 d	Hypotension Hypoglycaemia	First dose	3 mo of treatment	Face
16	M	9 mo 6 d	Hypotension	First dose		Face
21	M	11 mo	Hypotension	First dose		Face
25	F	7 mo 10 d	Bradycardia	First dose		Face

peral neuropathy and bone growth delay, and are no longer used [15].

Surgical excision under general anaesthesia may be preferred if the lesion does not respond to medical treatment or if it bleeds, but this carries the risk of a disfiguring scar. When the lesion is flat, flash lamp-pumped pulsed-dye therapy (laser) is very effective in arresting the proliferation phase by closing the vessels and reducing the blood supply to the lesion. This procedure should be repeated after 1 month for it to be completely effective. It does not necessarily require anaesthesia, but perfect eye protection is mandatory.

The use of oral propranolol (a  $\beta$ -blocker) is a very effective, fast and revolutionary treatment, which has completely changed our attitude towards subglottic, infiltrative and ulcerative haemangiomas [7, 17]. Previously, the use of propranolol for the treatment of heart problems and increased arterial pressure was widely accepted. Now its use in the treatment of haemangiomas is also widely accepted since many publications have showed its efficacy, especially for subglottic haemangiomas, for which other treatments were disappointing with severe side effects. The fact that the endothelial cells of a haemangioma express receptors to  $\beta$ -blockers leads us to suspect that the mechanism of efficacy of this treatment is a decreased production of vascular endothelial growth factor (VEGF) and fibroblast growth factor- $\beta$  (FGF- $\beta$ ). The therapeutic effect of propranolol includes vasoconstriction, inhibition of angiogenesis and induction of apoptosis in capillary endothelial cells [17, 18].

As previously reported, the most common dosage of propranolol was 2 mg/kg/day. This has proved to be safe and effective, with very few side effects [12]. Other papers advocate a daily dosage of 1 to 3 mg/kg/day, administered in three doses. A progressive dosage is usually recommended at the beginning of the treatment [10]. In our study, daily doses of 2 mg/kg were given orally to all patients during the proliferation phase. Two of our children were kept on a dosage of 1 mg/kg/day because of hypotension at this dose, but even on this lower dosage, the effectiveness on the haemangioma was already obvious after the second day. In our study, we wanted to keep the same dosage and same protocol for all children in order to diminish bias. However, for these two children, the decrease of blood pressure and the fast and excellent response at the initiation of the treatment convinced us not to increase the dosage to 2 mg/kg/day. We are under the impression that 1 mg/kg/day of propranolol is sufficient to treat haemangioma but to prove it we would need to create two groups of children in a randomised study with two different doses per kilogram in order to determine if the response to the propranolol treatment is dosage dependent or not.

The side effects of  $\beta$ -blocker treatment reported in the literature are asymptomatic hypotension, bradycardia, bronchospasm, hypoglycaemia and hyperkalaemia. It is therefore recommended that very young babies undergoing this treatment be hospitalised and subjected to blood glucose checks, cardiac ultrasound investigations and monitoring of vital signs (cardiac frequency and arterial pressure). Other complications such as insomnia, somnolence, cool or mottled extremities, diarrhoea and hair loss are less frequent and less dangerous [13]. An increasing number of

publications confirm the absence of adverse effects, even in low birth weight newborns. Of the 85 articles presented at an American conference in Chicago in 2011, 48 reported no complications in any patient [10]. Treatment of outpatients with monitoring seems to be possible for children older than 8 weeks. Hospitalisation is suggested for infants of less than 8 weeks or for children with comorbid conditions affecting the cardiovascular or respiratory system [10]. At the same conference, it was stipulated that echocardiography as a routine screening tool is not necessary in the absence of abnormal clinical findings. Pretherapeutic assessment, including ECG, echocardiography and blood examinations, seems to be necessary only in some cases, such as known bradycardia, a family history of congenital heart conditions or arrhythmias. Betloch-Mas et al. recommend that children be checked 5 hours after receiving the first dose [19]. A 48-hour hospitalisation for the initiation of propranolol therapy is nevertheless very expensive (from 2160 to 2540 CHF [2800–3200 €]).

According to our Swiss protocol, treatment was started at the hospital with continuous observation by nurses during 48 hours, irrespective of the age of the child [11]. Median age at the initiation of the therapy was 3.5 months. In three cases, we started the treatment after the end of the "theoretical" proliferative phase (9, 11 and 12 months of age). The results of this treatment were excellent in two cases and moderate in the third case. There is still no evidence concerning the optimal length of treatment in these exceptional cases [18].

All patients were assessed before treatment was initiated. Follow-up consisted in routine assessments by both our team and by the patient's own paediatrician to determine any necessary dosage adjustments. We adapted the dosage per kilogram up until 10 months of age, then gave half the dosage at 11 months and stopped the treatment at 12 months, in spite of the lack of evidence concerning the benefit of a progressive dosage decrease [20, 21]. The great majority of infants treated for IH in our study did not present any side effects. No insomnia, somnolence, cool or mottled extremities, diarrhoea or hair loss occurred. The transient hypotension and bradycardia seen in six of our patients (table 2) did not prevent the continuation of the treatment at a dosage of 2 mg/kg/day, except for two babies who were kept on a dosage of 1 mg/kg/day. Only one of our patients developed hypoglycaemia. We find that giving propranolol with meals is an effective precaution for avoiding this particular side effect.

## Conclusions

This study shows that although side effect reactions may occur after the first dose of the drug, they are not severe. Nevertheless, we had two children with a lower heart rate after the first dose of the drug and four children with a transient decrease of blood pressure (15% of mean arterial pressure), for two of whom we kept the dosage of 1 mg/kg/day as the effectiveness on the haemangioma was excellent. In view of these results, there will be a discussion in our "National Grand Round for Vascular Anomalies in Childhood". The 48-hour hospitalisation for the initiation of propranolol therapy seems to be not necessary as long as

contraindications to the drug and strict monitoring after the first dose are adhered to.

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## Figures (large format)

**Figure 1**

Infantile haemangioma of the face at 2 months (left) and after 2 weeks (right) of treatment with propranolol (2 mg/kg/day).

**Figure 2**

Two examples of genital area haemangiomas complicated by ulceration. Left: before treatment. Right: after treatment with propranolol (2 mg/kg/day).