

Propranolol: Effectiveness and Failure in Infantile Cutaneous Hemangiomas

Andrea Domenico Praticò^{1,2} · Filippo Caraci^{3,4} · Piero Pavone⁵ · Raffaele Falsaperla⁵ · Filippo Drago⁶ · Martino Ruggieri¹

Published online: 9 June 2015

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Abstract Infantile hemangiomas (IHs) occur in early infancy and are considered to be one of the most frequent childhood tumors. Poor responsiveness to the treatment and complications are reported in about 10 % of patients. For years, the most common treatments for cutaneous and complicated IHs were corticosteroids, interferon- α , vincristine, laser therapy, or surgical intervention. More recently, treatment with propranolol has been reported with high success rates, both in the cutaneous and complicated form of IHs, and it is now considered to be the first-line treatment for IHs. Herein we report five cases of cutaneous IHs who presented at our unit between January 2011 and June 2012: in three of five patients, the lesion improved soon after the beginning of propranolol treatment; one case presented slow but complete resolution; and in one patient the treatment was unsuccessful. Patients who do not respond to propranolol have been seldom reported in the literature. However, the failure of propranolol treatment in childhood hemangiomas has been more frequent in our

experience than that reported in previous case series. More attention should be given to the cases that poorly or negatively respond to treatment, and to the mechanisms underlying the failure to respond to treatment with propranolol.

Key Points

Treatment with propranolol has been reported with successful results in the cutaneous and complicated forms of infantile cutaneous hemangiomas and it is now considered to be the first-line treatment for this disorder.

In four of five children treated in our center, propranolol therapy has led to the resolution of the hemangioma, while in one patient it did not give appreciable results.

Worldwide, this therapy does not reach significant results in about 10 % of patients, with re-growth, slow improvement, or failure. The causes of this therapeutic failure have yet to be investigated and further study should be dedicated to this relevant question.

✉ Andrea Domenico Praticò
terrenere178@tin.it

¹ Department of Clinical and Experimental Medicine, University of Catania, Via S. Sofia 78, Catania, Italy

² Department of Clinical and Molecular Biomedicine, University of Catania, Catania, Italy

³ Department of Educational Sciences, University of Catania, Catania, Italy

⁴ IRCCS Associazione Oasi Maria S.S., Institute for Research on Mental Retardation and Brain Aging, Troina, Enna, Italy

⁵ Unit of Pediatrics and Pediatric Emergency “Costanza Gravina”, University-Hospital “Vittorio Emanuele-Policlinic”, Catania, Italy

⁶ Chair of Pharmacology, Department of Clinical and Molecular Biomedicine, University of Catania, Catania, Italy

Introduction

Infantile hemangiomas (IHs) occur with a high frequency in childhood and represent one of the most common tumors of infancy. IHs predominantly affect the female sex,

caucasians, twins, and premature infants [1]. The lesions may be located in the skin or internal organs, and the most frequent complications are infections and ulceration with necrosis and bleeding.

IHs are located on the face and neck in approximately 60 % of patients, causing severe disfigurement, followed by the trunk (25 %) and the extremities (15 %) [1]. IHs located in the brain, airways, eye, lumbosacral region, and liver are particularly dangerous because of the risk of complications and difficulties in their treatment [2]. IHs manifest in the first weeks of life, with a rapid proliferative growth that lasts for some months followed by a progressive regression over a period of months or years. Involution occurs completely in 50 % of patients by the age of 5 years and in 90 % by 9 years of age [3].

If localized in the skin, in most cases this condition shows a benign clinical course with complete resolution; conversely, in about 10 % of patients, poor responsiveness to treatment and complications are reported that are related to the size, type, and localization in certain organs, such as the liver, brain, larynx, and small and large intestine [4].

In 1988, we reported a 3-month-old patient with a massive, aggressive mixed hemangioma, localized on right side of the face with ulceration of the ear lobe and nasal septum, associated with cerebral and cerebellar malformations, who died at 4 months of age despite treatment with corticosteroids [5]. Conversely, we have also reported an infant with cutaneous and leptomeningeal diffuse hemangioma who had a rapid and benign course with regression of the lesion in the first year of life [6].

Many types of treatment have been proposed for the cutaneous and complicated forms of IHs—systemic or intralesional corticosteroids, interferon- α , vincristine, laser therapy, or surgical intervention—but treatment with propranolol has recently been reported to have successful results in the cutaneous and complicated forms of IHs and it is now considered the first-line treatment for IHs [1, 7–9].

Here, we report on five children affected by cutaneous IHs localized in different areas of the face. In four, treatment with a standard dosage of propranolol resulted in resolution of the lesions. In one, failure to respond to treatment was observed.

Cases Presentation

Familial and personal histories were carefully recorded for the IH patients and an accurate clinical examination was performed at the beginning of treatment, together with laboratory tests (including complete blood count and coagulation assay), blood pressure, electrocardiogram (ECG) and echocardiogram, abdominal ultrasounds, and in some cases brain magnetic resonance imaging (MRI).

During the treatment, blood pressure evaluation was frequently performed and an ECG and heart ultrasound were carried out every 3 months.

All patients were recruited between January 2011 and June 2012 and started treatment with propranolol (starting dosage 1 mg/kg/day and rapidly reaching the dose of 2 mg/kg/day) only after parental informed consent. The off-label use of propranolol was proposed to parents according to research published in international peer-reviewed journals [1, 7–9] described in the informed consent and in accordance with Italian legislation [Article 3(2) of Law 94, 1998]. Treatment was continued at home and the child was reevaluated after 10 days and then every month.

Dimensions, color, consistency, and photographic documentation based on visual analog scale (VAS) were recorded before and periodically after starting treatment. A minimum 75 % improvement with no regrowth up to 1 month after stopping treatment was considered as success. Propranolol was prepared by the hospital pharmacy as a capsule containing a mixture of propranolol and mannitol.

Case 1

A 2-month-old girl was referred to our unit with a cavernous non-ulcerated, non-hemorrhagic hemangioma involving the left forehead and the superior part of the nose, measuring 7×4 cm. General conditions were good, and she was breast-fed. Treatment with propranolol was started in the following days. Significant reduction in size and discoloration were seen within 2 months. The treatment was stopped at the age of 1 year with resolution of the hemangioma and a small residual scar. At the present time, at the age of 30 months, she does not present recurrence of hemangioma.

Case 2

A 3-month-old girl came at our unit for observation for a cavernous hemangioma localized in the anterior part of the left forearm, measuring 6×3 cm. Propranolol was started at this age and the girl was treated for a period of 12 months: improvement of the lesion was observed 1 month after the beginning of treatment, initially with a significant discoloration and then with a reduction in size (within 2 months). At the follow-up at 18 months of age, a residual scar surrounded by normal skin was observed.

Case 3

A 3-week-old boy presented with a facial hemangioma involving the ear lobe and nasal septum. The treatment was started at this age. The initially improvement consisted only in a discoloration, which was noticed after 1 month. The resolution was slow and complete regression of the

lesion was seen at 15 months of age. At the follow-up at 24 months of age, no regrowth of the lesion was observed.

Case 4

A 10-month-old girl presented for examination for facial hemangioma localized in the left cheek, measuring 4×2 cm, which was initially treated at the age of 3 months with prednisone 1 mg/kg/day. A slight initial improvement was reported and consisted in a minimal, non-significant reduction in the size of the lesion. Therefore, treatment with the corticosteroid was stopped and propranolol was initiated at the age of 4 months. One month later, the girl showed a clearer coloration of the lesion and also a reduction in its size. After 8 months, there was an almost complete resolution of the lesion. At the follow-up at 25 months of age no regrowth of the lesion was observed.

Case 5

Case 5 was a girl who was the second born of healthy parents, aged 29 and 28 years. Her brother was healthy. No cases of hemangioma were present in the family, and the pregnancy was normal. The girl was born prematurely at 32 weeks of gestation with a birth weight of 1850 g. In the first day of life she presented mild respiratory distress due to the prematurity, and for the first month of life she was placed in an incubator. The presence of a small hemangioma in the middle of the chin was noticed at 6 days of life, and it rapidly enlarged over a period of 2 months. At the age of 3 months, the girl came to our observation. She showed a 'beard hemangioma' involving all of the chin and extending to the lower lips (Fig. 1). The hemangioma caused bleeding, especially during bottle feeding. A dorsal thoracic hemangioma, less relevant in size, was also present. Treatment with propranolol was started at a dosage of 1 mg and then increased to 2 mg/kg/day. We followed up



Fig. 1 Patient 5 at 3 months of age: 'beard hemangioma' involving all of the chin and extending to the lower lips. It is possible to notice ulceration that had caused bleeding, especially during bottle feeding

the girl every month: in the first month, an improving in the ulcerative lesion and of its bleeding was observed, together with a little discoloration, but after this period, although propranolol treatment was continued, no improvement was observed. At the age of 12 months, when the treatment was stopped, the lesion was still the same size and color as at the beginning of treatment.

At the time of writing, the girl is 19 months old. On physical examination, her general condition is quite good: weight 9 kg (25th centile), head circumference 46 cm (25th centile), and height 75 cm (25th centile). The beard hemangioma is red-vinaceous in color, 7×5 cm large, presenting a wrinkled surface and involving the chin entirely (Fig. 2). The dorsal thoracic hemangioma is also unmodified. Of note, the girl shows a pre-auricular cutaneous appendix, but no other anomalies are present.

Discussion

The five patients reported here showed strawberry hemangiomas localized mainly in the face and in one patient on the arm. As reported elsewhere, those of female

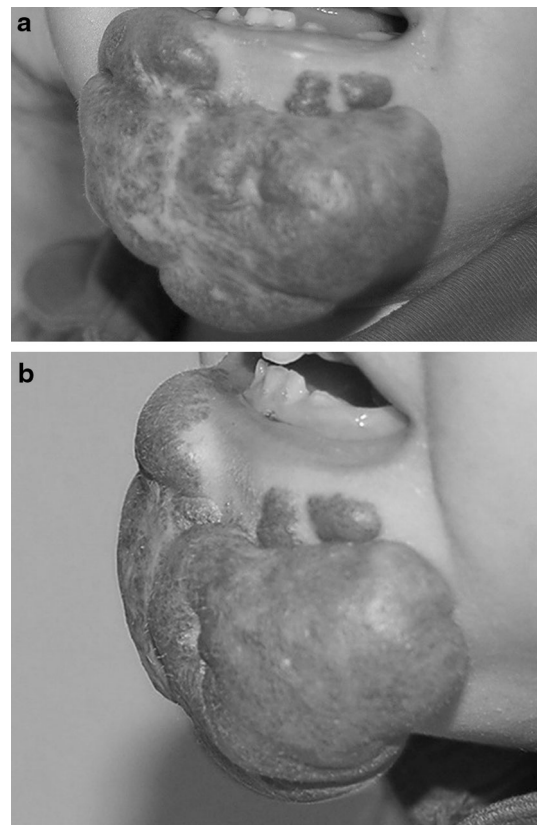


Fig. 2 Patient 5 at 19 months of age: the 'beard hemangioma' is red-vinaceous in color, and of the same size as at the start of treatment (7×5 cm). The hemangioma presents a wrinkled surface and involves entirely the chin

sex were the most affected with a ratio of 4:1. Among these five patients, only one was born prematurely. No positive familial history was reported and no complication during pregnancy was recorded.

In all of the patients, the cutaneous lesion was seen after birth with a rapid growth in the first months of life. The anomalies involved the skin and presented in four of five cases as isolated cutaneous lesions; only patient 5 showed a further localization on their back and a minor malformation consisting of a small pre-auricular cutaneous appendix. In four patients, the treatment was performed with propranolol only. Patient 4 had started treatment with corticosteroids, but propranolol was then employed due a lack of effect. The response to the treatment in our patients was good and rapid in three, slow in one, and unsuccessful in one. This last patient is now a candidate for surgical treatment. No adverse effects were recorded in the children during the period of treatment with propranolol.

The efficacy of propranolol in healing IHs has been well-documented in the literature as single case reports, case series, reviews, and meta-analyses (Table 1) [8, 10–15]. Hemangiomas are made up of various types of cells, including endothelial cells. Capillary endothelial cells are known to express β_2 -adrenergic receptors [16] and propranolol is a β -adrenergic receptor antagonist, initially developed for the treatment of cardiac diseases (angina, infarction, hypertrophic cardiomyopathy, arrhythmias) and hypertension. Propranolol is orally supplied and reaches its peak plasma concentration 1 or 2 h after intake. Its half-life is 3–6 h, with rapid distribution in the lungs, kidneys, and heart. It is 80–95 % bound to protein and metabolized in the liver [17]. In 2008, Léauté-Labrèze et al. [1] reported the efficacy of propranolol in patients with IHs. Since that year, a large number of studies have reported the efficacy of this treatment in patients affected by IHs, with good tolerance and few adverse effects. The mechanism of action of propranolol in the IHs is not completely understood, but effects on vasoconstriction, a down-regulation of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF), and stimulation of apoptosis of capillary endothelial cells have been proposed [18–20]. In particular, Zhang et al. [21] have demonstrated that propranolol inhibits the angiogenesis by reducing both VEGF synthesis and release in hemangioma-derived stem cells. In their experimental model, propranolol did not inhibit proliferation or promote apoptosis of hemangioma-derived stem cells isolated from IH patients, but suppressed the expression of VEGF and bFGF in vitro. Morphological, histological, and immunohistological improvement were observed in vivo in murine models. In propranolol pretreated hemangioma stem cells, mean micro-vessel density

significantly decreased and protein levels of VEGF markedly decreased, while bFGF was still detectable.

The role of propranolol on the stimulation of apoptosis has been questioned by Kum and Khan [22], in whose experiment propranolol significantly reduced hemangioma stem cell growth but failed to induce the activation of caspase-3, which plays a central role in the execution phase of cell apoptosis.

On the contrary, in another study, exposure of hemangioma endothelial cells to propranolol resulted in typical apoptotic morphological changes, including shrinkage, formation of apoptotic bodies, retention of plasma membrane integrity, and, finally, in a marked increase of caspase-8, cytochrome c, apoptosis-inducing factor, caspase-3, and poly (ADP-ribose) polymerase 1 [23]. A recent hypothesis concerns the action of propranolol on the renin-angiotensin system (RAS), which may have an important role in the mechanism of action of propranolol [13, 18, 24, 25]. Ultimately, as reported by Ji et al. [26], it is likely that the anti-hemangioma effect of propranolol may not be attributable to a single mechanism, but rather to a combination of events, including pericyte-mediated vasoconstriction, inhibition of vasculogenesis and catecholamine-induced angiogenesis, and the disruption of hemodynamic force-induced cell survival and the RAS.

The adverse effects reported with the use of this drug are usually mild, presenting in most cases as gastrointestinal symptoms, sleep disturbances, and lethargy. Broeks et al. [12], who employed propranolol in the treatment of airways hemangiomas, reported adverse effects in only four of 81 patients: two presented mild gastrointestinal symptoms and two experienced pulmonary symptoms. In the literature, severe adverse effects include hypoglycemic events, hypotension and bradycardia, and bronchospasm and wheezing in asthmatic patients [27–29].

Several studies demonstrate the efficacy of propranolol in the treatment of IHs. A better effect of propranolol than of corticosteroids in the treatment of IHs has been confirmed by the randomized controlled study by Malik et al. [11] in a sample of 30 patients and in a retrospective study by Hermans et al. [15] in 174 patients. In 58 children treated with propranolol at dosage of 1–1.5 mg/kg/day, Qin et al. [30] reported excellent results in 17.2 %, good in 60.4 %, moderate in 20.7 %, and poor results only in 1.7 %. Buckmiller et al. [31] in their experience of 32 patients (dosage 2 mg/kg/day), reported excellent results in 50, 47% partial responders, and 3 % no responders. Large reviews of propranolol treatment for life-threatening airway IHs have been performed by Starkey and Shahidullah [32], Broeks et al. [12], and Lou et al. [13]. Starkey and Shahidullah [32] focused their attention particularly on the adverse effects of propranolol and advise limiting the use of this treatment only

Table 1 Case series of patients affected by infantile hemangiomas and treated with propranolol

		References									
		Léauté-Labrèze et al. [1]	Qin et al. [30]	Sans et al. [43]	Buckmiller et al. [31]	Georguntzou et al. [29]	Melo et al. [14]	Broeks et al. [12]	Malik et al. [11]	Hermans et al. [15]	Present series 2015
Number of patients	15 (4 treated with propranolol, 11 with corticosteroids)	58	32	32	32	28	6	5	30 (three groups: A—propranolol; B—corticosteroids; C—both)	174	5
Sites	Skin	Skin	Skin	Skin	Skin; airway	Skin	Skin	Airway	Skin	Skin	Skin
Age at initiation	4–6 months	4 months	4.2 months (mean)	4.2 months (mean)	4.9 months (mean)	5.95 months (mean)	2–6 months	3 weeks to 6 months	A: 4.6 months (mean) B: 5.5 months (mean) C: 4.7 months (mean)	4.8 months (mean)	3 weeks to 4 months
Dosage of propranolol (mg/kg)	2–5	1–1.5	2–3	2	2	2	2	2.2–3	2–3	2–3	2
Duration of treatment (months)	8.7 (mean)	2–5	6.1 (mean)	6–18	6–18	7.56 (mean)	6–18	9–19	A: 9.9 (mean) B: 13.25 (mean) C: 9.5 (mean)	10.7 (mean)	6–10
Outcome	Evident improvement in 100 % of patients treated with propranolol	Excellent results in 17.2 %, good in 60.4 %, moderate in 20.7 %, and poor in 1.7 %	Evident improvement in 100 %	Excellent results in 50 %, partial response in 47 %, no response in 3 %	Excellent results in 85.7 %; regrowth in 14.3 % after propranolol discontinuation	Excellent results in 85.7 %; regrowth in 14.3 % after propranolol discontinuation	Evident improvement in 100 %	Evident improvement in 100 %, permanent effect after discontinuation in 80 %	Mean initial response time in A and C significantly lower than B. Significant change in consistency very early in A (24 h) compared to B and C (8 days). Visual analog scale improvement more evident in A and C than B	Evident improvement in 99.4 %	Evident improvement in 80 %; no response in 20 %
Adverse effects	None	Bradycardia (100 %), diarrhea (63.8 %), and sleep change (30.2 %)	Wheezing (3 %)	Somnolence (27.2 %), gastroesophageal reflux (9.1 %), respiratory syncytial virus exacerbation (4.5 %), and rash (4.5 %)	Hypotension (14.3 %)	None	Wheezing in 1 out of 5 patients (20 %)	None	2 Patients in A presented adverse effects, 1 hypoglycemia, 1 somnolence, and continued treatment at 1 mg/kg	Cold extremities (36.2 %), nocturnal restlessness (22.4 %), wheezing (9.2 %), and hypotension (3.4 %)	None

to complicated hemangiomas, underlying that further research should be conducted regarding the safety and efficacy of the treatment. Broeks et al. reported their personal experience in five patients with IHs in the airways treated with propranolol: four had a rapid positive response and only one patient had a relapse of hemangioma with complete resolution after the new cycle of treatment. In their case series and review of the literature involving a total of 81 patients with airway hemangiomas, these authors reported an overall good response in 90 % of the patients. In some non-responders, dose adjustment or restarting the therapy was effective: only one patient was shown to be resistant to the treatment [12]. In a recent comprehensive meta-analysis, Lou et al. reviewed and compared the results of 35 studies involving 324 patients overall who were affected by IHs. The efficacy of propranolol was higher than the other known treatments such as corticosteroids, vincristine, and laser. Propranolol was more efficacious than the other treatments for all of the types of pediatric hemangiomas (cutaneous, periocular, airway, and hepatic) [13].

Our results confirm the efficacy of propranolol as the gold standard procedure in the treatment of cutaneous IHs, including appreciable aesthetic results with an evident improvement obtained in four out of five patients.

Nevertheless, there are a number (about 9 %) of IH patients in whom re-growth, minimal improvement, or treatment failure are reported [12]. Recurrence of IHs after discontinuation of propranolol has been reported by Chang et al. [33] in two children and by Georgountzou et al. [29] in three out of 28 children. Re-growth of IHs has been reported to occur 2–3 weeks after treatment suspension and usually responds to the re-introduction of propranolol [8, 34, 35]. A minimal improvement has been reported in several studies [36–41], but in most of these cases the hemangiomas were localized in internal organs other than the skin or the lesions were particularly wide.

Concerning treatment failure, in a large observational study of 1130 patients treated with propranolol, only ten patients (0.9 %) did not respond to propranolol and were classified as “propranolol-resistant”. The treatment failure was not related to early treatment or to the proliferation stage [42].

The reason for some patients with cutaneous IHs not responding to propranolol is a matter of debate. It is reasonable to presume that ulceration may reduce the effect of propranolol treatment in cutaneous hemangiomas. In fact, in a series of 30 patients with ulcerate hemangiomas, Manunza et al. [20] reported that ten patients with smaller lesions had good results while the patients with deeper ulcerations did not respond to treatment. Conversely, in a patient reported by Malik et al. who had a large scapular hemangioma, treatment with propranolol resulted in interruption of the bleeding in 24 h and healing of ulcer within 3 months [11]. Excellent results were also obtained by

Melo et al. [14] in a 5-month-old boy with a left arm hemangioma presenting with a lateral ulceration, by Sans et al. [43] in 32 patients where the lesion healed within 2 months, and also by Kim et al. [44] and Naouri et al. [45]. In our patient for whom the treatment failed, the ulceration had a rapid improvement soon after the start of the treatment but the lesion remained unmodified in size and color. Moreover, the therapy did not reduce the lesion on their back, which was not ulcerated.

The reason for the non-responsiveness to propranolol may have other explanations. In some cases, the β -receptors in affected patients could theoretically be absent or reduced in numbers, thus leading to a non-responsiveness to the drug. Broeks et al. [12] hypothesized a resistance to β -blockers as the reason for the missed response of some hemangiomas to propranolol. It must be also underlined that poor compliance by the parents may be the reason for the treatment failure in cutaneous hemangiomas.

Conclusions

To our knowledge, our patient is one of the uncommon cases of cutaneous hemangioma that is non-responsive to propranolol. We presume that the failure of this treatment in cutaneous hemangiomas is more frequent than the rare cases reported in the literature. The excellent effect of propranolol on patients with cutaneous or complicated hemangiomas has been clearly demonstrated, but we believe that more attention should be given to cases that poorly or negatively respond to treatment.

Acknowledgments Written informed consent was obtained from the caregivers of each of the patients for publication of the information and accompanying images included in this case series. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Andrea Domenico Praticò, Filippo Caraci, Piero Pavone, Raffaele Falsaperla, Filippo Drago, and Martino Ruggieri declare that they have no conflict of interest. No financial support was received for the conduct of this study or preparation of this manuscript.

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