RESEARCH

Management of infantile hemangiomas—experience of a tertiary hospital

Rita Gomes[1] · Luís Salazar[1] · Carolina Fraga[1] · Mário Rui Correia[2] · Joana Barbosa-Sequeira[3] · Alexandre Fernandes[1] · Sílvia Álvares[4] · José Banquart Leitão[2] · Margarida Paiva Coelho[1]

Abstract

The purpose of the study is to describe the experience of a multidisciplinary team in a tertiary hospital regarding the management of Infantile Hemangiomas (IH). The method employed is a retrospective analysis of patients with IH followed in a tertiary pediatric hospital between January 2010 and May 2022. A total of 393 IH were diagnosed (56.7% female), with a median age of 5 months (interquartile range (IQR), 3–10). Imaging investigation was necessary for diagnosis and for exclusion of other IH in 9.2% and 14.3%, respectively. Focal (74.0%) and superficial (59.7%) lesions were more frequent as was facial location (35.9%). Pre-treatment ulceration or hemorrhage occurred in 6.6%. At follow-up, 87.4% regressed partially and 12.6% completely; 2.7% relapsed. Propranolol was started in 30.0% of cases for a median period of 9 months (IQR, 6–12), mainly due to esthetic concerns (41.9%). Side effects occurred in 8.3% (sleep disturbance in 5.1%). Only 1.7% were refractory and 5.9% had a rebound effect. Eleven patients were treated with topical timolol and 41 underwent surgery. Patients that were treated with propranolol had more risk factors ($p = 0.016$) and presented deeper lesions ($p < 0.001$) with a larger diameter ($p < 0.001$); total IH regression was less frequent ($p < 0.001$). Since 2020, twice-daily dosage was more frequently prescribed than three times daily ($p = 0.007$) and inpatient initiation of propranolol decreased ($p = 0.750$), without significant difference in the incidence of adverse reactions, duration of treatment, and lesion evolution.

Conclusions: Our protocol proved to be safe and feasible in an outpatient setting and twice daily administration of propranolol was effective. The majority of IH showed at least partial regression. Early detection of high-risk IH is paramount and a multidisciplinary assessment by a specialized team is essential for adequate management.

What is Known:
• *IH are the most common vascular tumors in childhood. Although the majority evolves favorably, treatment may be warranted in selected cases.*
• *Early detection of high-risk IH is paramount, and a multidisciplinary assessment by a specialized team is essential for adequate management.*

What is New:
• *One-third of our sample was treated with propranolol. These patients had more risk factors and presented deeper lesions with a larger diameter, and tumor total regression was less frequent.*
• *Our results reinforce safety and feasibility of propranolol initiation in an outpatient setting, including twice daily dosage.*

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✉ Rita Gomes
ritagomesmoreira02@gmail.com

1 Pediatrics Department, Centro Materno Infantil Do Norte Albino Aroso, Centro Hospitalar Universitário Do Porto (CMIN-CHUPorto), Porto, Portugal

2 Pediatric Surgery Department, Centro Materno Infantil Do Norte Albino Aroso, Centro Hospitalar Universitário Do Porto (CMIN-CHUPorto), Porto, Portugal

3 Pediatric Surgery Department, Centro Hospitalar Universitário São João, Porto, Portugal

4 Pediatric Cardiology Department, Centro Hospitalar Universitário Do Porto (CMIN-CHUPorto), Unit for Multidisciplinary Research in Biomedicine (UMIB), School of Medicine and Biomedical Sciences (ICBAS), Centro Materno Infantil Do Norte Albino Aroso, Porto, Portugal

Abbreviations

ECG	Electrocardiography
IH	Infantile hemangiomas (IH)
LUMBAR	Lower body IH, urogenital anomalies/ulceration, myelopathy, bony deformities, arterial anomalies, renal anomalies
MRI	Magnetic resonance imaging
PHACE	Posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies

Introduction

Infantile hemangiomas (IH) are the most common benign vascular tumor in children, with an estimated prevalence of 4–5%, being more frequent among Caucasian infants and in females [1–5]. Prematurity, low birth weight, multiple gestation, older maternal age, pre-eclampsia/placenta previa, and family history are known risk factors [3, 6]. Most IH are solitary and superficial and can occur anywhere on the skin, mucous membranes, and viscera despite being more common in the head and cervical region [4], [7–9]. Pathophysiology isyet to be completely understood but IH appear to be the result of adysregulation of both vasculogenesis, and angiogenesis and multiple studiessuggest that hypoxia may have a key role [10–13].

The natural history is distinctive from other congenital vascular malformations. IH generally appear within the first days to weeks of life and then grow continuously during the first year. However, precursor lesions may be present at birth or manifest during the early neonatal period as a pale area or a telangiectatic red macula [10, 14, 15]. The proliferative phase is followed by a spontaneous involution phase that typically begins after 1 year and lasts a variable number of years [10, 16]. In the absence of treatment, 50–70% of children will have residual lesions, such as scarring, atrophy, redundant skin, discoloration, and telangiectasias [10, 16–18].

The author's aim was to characterize a sample of patients with IH followed in a tertiary hospital and to describe our experience regarding their management. We aimed to assess the prevalence of children that underwent treatment with oral propranolol, as well as its' efficacy and safety profile, and the proportion of patients submitted to surgery. Finally, we tried to evaluate the application of our hospital protocol, which was revised and updated in 2020 and simplified initiation of treatment and posology.

Managementapproach should be individualized, based upon the IH characteristics and phaseof evolution, the presence or possibility of complications, and the age of thepatient [3], [8]. The diagnosis is mainly clinical [10]. A watchful waiting approachis recommended in the majority of cases that evolve favorably, with periodicfollow-up complemented by serial photography. However, an infant with actual orpotential risk for complications should be referred to a specialized tertiarycenter for evaluation by a multidisciplinary team for specific diagnosticwork-up and possible treatment initiation [8]. Oral propranolol has become thetreatment of choice for problematic IH, as it is both effective and safe[19–21]. In selected cases, other therapeutic options may be considered.

Materials and methods

Study design and sample

We conducted an observational retrospective, descriptive, and analytical study. All pediatric patients with the diagnosis of IH followed in the outpatient department of our tertiary hospital between January 2010 and May 2022 were included. All patients submitted to IH's surgical removal in whom the anatomopathological examination revealed an alternative diagnosis were excluded.

Data collection and variable definition

Data was collected by assessing the patients' electronic clinical files. Demographic variables including sex and age at diagnosis and at treatment were collected. Delay to first evaluation was defined as the period of time between the date when the lesion was first noticed or the date of referral and the date of first appointment. Delay to diagnosis was defined as time between the first hospital visit (including pediatric, pediatric cardiology, and pediatric surgery appointments) and diagnosis.

Data on IH characterization and natural history was also collected (location and size of the lesion, risk factors, associated syndromes or comorbidities, and complications). IH were classified according to tissue penetration (superficial, deep, and combined) and distribution (focal, two to five lesions, segmental, multiple, and undetermined). The work-up for confirmation of diagnosis and/or exclusion of other IH was reviewed, as well as the need for evaluation by specialists. Treatment approach is classified as pharmacological (propranolol and other drugs), laser, or surgery. Partial or total regression considered color, diameter, and, when applicable, depth improvement. Whenever possible, the lesions were photographed (with the caregiver's consent). Refractory IH was considered when there was no clinical improvement (color or size) following treatment. Relapse was defined as a lesion's regrowth after an initial partial or total regression [22].

Regarding propranolol treatment, the following data was collected: place of initiation (inpatient versus outpatient), dosage, duration, and adverse reactions. Rebound effect was defined as a darkening of the lesion and/or a size increase after propranolol suspension.

Hospital protocol for oral propranolol administration

Treatment with a manipulated solution of propranolol chloride (1 mg/mL or 5 mg/mL) was considered in infants with high-risk criteria (Fig. 1). Since the revision of the protocol in January 2020, a twice-daily dosage was adopted (rather than thrice daily). Verbal and written information about IH natural history, potential adverse reactions, and their management was carefully explained to caregivers.

Ethics

This research complies with all the relevant national regulations and institutional policies and is in accordance to the tenets of the Helsinki Declaration. The study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto and Institute of Biomedical Sciences Abel Salazar.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics 27.0. Continuous variables are expressed as median and interquartile range (IQR). Differences between groups in continuous variables were evaluated with independent sample t test. Differences in the distribution of categorical variables were evaluated with chi-square tests and ANOVA. All p values are two-sided and were considered statistically significant if < 0.05.

Results

The sample baseline characterization is described in Table 1. A total of 393 patients were diagnosed with IH. Most were referred by general family clinicians ($n = 150$; 38.7%) or other hospitals ($n = 124$; 32%). Delay to first appointment and to diagnosis was 1 (IQR, 1–4) and 0 months (IQR 0–0), respectively. Fifty-nine (15.0%) patients had risk factors: prematurity ($n = 54$; 13.7%) and low birth weight ($n = 42$; 10.7%). Significant comorbidities such as cardiopathy ($n = 11$; 2.8%) and other malformations ($n = 7$; 1.8%) were present in 5.9%. Tumor locations are listed in Table 1; there were no IH exclusive of the airway or liver in our sample. IH were more frequently superficial ($n = 227$; 59.7%) and focal ($n = 289$; 74.1%). Imaging investigation with lesion ultrasound with Doppler was necessary for diagnosis in 36 (9.2%) patients; abdominal ultrasound with Doppler or resonance angiography was performed in 63 (16.0%) patients for exclusion of other IH. Thirty (7.7%) patients exhibited 32 complications prior to treatment initiation, the more common being ulceration
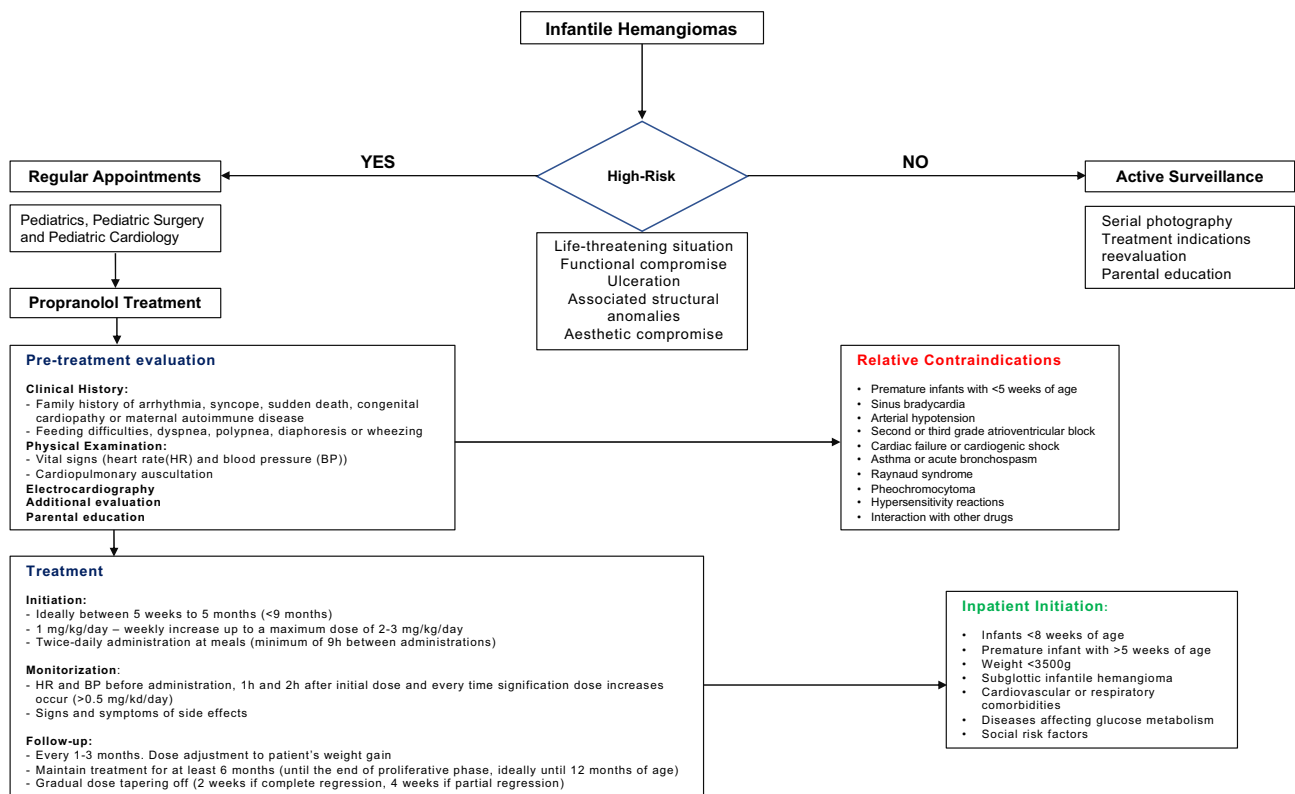

Fig. 1 Hospital protocol for oral propranolol administration

Table 1 Sample baseline characterization. Legend: *M* months, *IQR* interquartile range, *US* ultrasound, *MRI* magnetic resonance imaging, *IH* infantile hemangioma

Total	393
Male:female	1:1.3
Median age at diagnosis (M)	5 (IQR 3–10)
Maximum median diameter of IH (cm)	2 (IQR 1.4–3.0)
Provenience	
General family clinicians	150 (38.7%)
Other hospital services	91 (23.5%)
Ward	17 (4.4%)
Other hospitals	124 (32%)
Emergency department	6 (1.5%)
Location	
Face	141 (28.8%)
Scalp	67 (13.7%)
Trunk	134 (27.4%)
Perineum	38 (7.8%)
Limbs	94 (19.2%)
Cervical	15 (3.1%)
Classification	
Superficial	227 (59.7%)
Deep	51 (13.4%)
Combined	102 (26.8%)
Classification	
Focal	289 (74.1%)
2–5 lesions	86 (22.1%)
Segmental	5 (1.3%)
Multiple	10 (2.6%)
Risk factors	59 (15.0%)
Prematurity	54 (13.7%)
Low birth weight	42 (10.7%)
Multiple gestation	11 (2.8%)
Obstetric conditions	11 (2.8%)
Family history	1 (0.3%)
Comorbidities	23 (5.9%)
Other malformations	7 (1.8%)
Cardiopathy	11 (2.8%)
Others	5 (1.3%)
Complications	32 (8.1%)
Ulceration	25 (6.3%)
Pain	3 (0.8%)
Bleeding	4 (1.0%)
Investigation work-up	
Lesion (Doppler) US	36 (9.2%)
Abdominal (Doppler) US	46 (11.7%)
Electrocardiogram	136 (34.6%)
Echocardiogram	136 (34.6%)
MRI angiography	17 (4.3%)
Ophthalmological evaluation	20 (5.1%)
Coagulation study	1 (0.3%)
Thyroid function tests	2 (0.5%)

Table 1 (continued)

Total	393
Management	
Propranolol	118 (30.0%)
Timolol	11 (2.8%)
Deflazacort	1 (7.1%)
Hydrocolloid	2 (14.3%)
Surgery	41 (10.4%)
Laser	3 (0.8%)
IH evolution	
Color	149 (96.1%)
Diameter	150 (95.5%)
Deepness	76 (93.8%)
Regression	
Partial	160 (87.4%)
Total	23 (12.6%)
Relapse	2 (2.7%)

($n = 25$; 6.3%). One hundred and eighteen patients were treated with oral propranolol, 11 (2.8%) were treated with topical timolol, 41 (10.4%) underwent surgery, and 3 (0.8%) were treated with laser therapy. Cases without indication for treatment were only reevaluated once, and those treated with propranolol had a median follow-up of 20 months (IQR, 12–42). During follow-up, 160 (87.4%) tumors regressed partially and 23 (12.6%) completely and 2 (2.7%) relapsed, one after propranolol and the other after surgery.

Table 2 shows the characteristics of the patients selected for oral propranolol treatment. The main indications for treatment were actual or risk for esthetic ($n = 49$; 41.9%) or functional ($n = 46$; 40.3%) compromise and ulceration ($n = 18$; 15.8%); one patient had PHACE syndrome (posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies). Treatment initiation before the age of 6 months was not significantly associated with better outcomes regarding color ($p = 0.608$), diameter ($p = 1.000$), deepness ($p = 0.180$), lesion regression ($p = 0.357$), and recurrence ($p = 0.729$). Significant adverse reactions occurred in 8.3% patients, more commonly sleep disturbance ($n = 5$; 4.6%) and bradycardia ($n = 3$; 1.8%). Only 1 (0.8%) was refractory to propranolol for which he underwent surgery. A rebound effect was observed in 6 (5.1%) patients despite gradual suspension.

Tables 3 shows a comparative analysis between patients that underwent treatment with only oral propranolol (group 1) and those in whom no medical treatment was performed (group 0). Patients from group 1 had more risk factors ($p = 0.016$) and presented deeper lesions ($p < 0.001$) with a larger diameter ($p < 0.001$). Total IH's regression was less frequent in group 1 ($p < 0.001$).

Table 2 Characterization of oral propranolol treatment. Legend: *M* months, *IQR* interquartile range

n	118
Place of initiation	
Outpatient	74 (69.8%)
Inpatient	32 (30.2%)
Median age at the start of treatment (M)	4 (IQR 3–6)
Median minimum dose (mg/kg/day)	1.3 (IQR 1.0–1.8)
Frequency	
Thrice daily	82 (87.2%)
Twice daily	12 (12.8%)
Indication for treatment	
Esthetic compromise	49 (41.9%)
Functional compromise	46 (40.3%)
Ulceration	18 (15.8%)
Associated syndromes	1 (0.9%)
Median duration of treatment (M)	9 (IQR 6–12)
Adverse reactions	9 (8.3%)
Sleep disturbance	5 (4.6%)
Bradycardia	2 (1.8%)
Bradycardia and sleep disturbance	1 (0.9%)

Since 2020, twice-daily dosage was more frequently prescribed ($p = 0.007$) and inpatient initiation of propranolol decreased ($p = 0.750$), without significant difference in the incidence of adverse reactions, treatment duration, and lesion evolution. The results of the comparative analysis between twice- and thrice-daily dosage are shown in Table 4.

Discussion

Consistent with what is reported in the literature, IH were more prevalent in females, mostly located in the face region and the majority were superficial solitary lesions [3, 8]. In our sample, the incidence of complications was lower than reported, with ulceration being the most prevalent. Previous studies stated that up to 12% of IH referred to pediatric centers were complex and prone to complications and that ulceration occurred in 10–25% [23]. Size, location, and type are determinants for ulceration, with large, superficial, and segmental tumors being substantially more likely to ulcerate [10].

Median delay to first appointment was 1 month, a relatively short period of time, not exceeding the window of opportunity during which evaluation and possible treatment would be of maximum benefit in most patients. Disease heterogeneity can make differential diagnosis challenging, especially for IH with limited or minimal growth and those with a deep component [8, 24, 25]. For this reason, in the case of diagnostic doubt, infants should be referred early for specialized consultation for

Table 3 Comparative analysis between patients selected for treatment with propranolol (group 1) and those in whom no medical treatment was performed (group 0). Legend: *cm* centimeters, *IH* infantile hemangioma

	Group 0 $n = 275$	Group 1 $n = 118$	p
Location			0.787
Face	21.6%	44.7%	
Scalp	15.6%	9.9%	
Trunk	30.7%	15.8%	
Perineum	8.6%	10.5%	
Limbs	22.2%	12.5%	
Neck	1.3%	6.6%	
Type			**< 0.001**
Superficial	67.6%	42.7%	
Deep	12.6%	15.4%	
Combined	19.8%	41.9%	
Classification			0.078
Focal	76.1%	69.2%	
2–5 lesions	21.3%	23.9%	
Segmental	0.4%	3.4%	
Multiple	2.2%	3.4%	
Risk factors	11.8%	21.4%	**0.016**
Complications	5.0%	10.3%	0.061
Mean size (cm)	2.1 (±1.2)	3.5 cm (±2.2)	**< 0.001**
IH evolution			
Color	95.7%	96.0%	0.922
Diameter	93.5%	98.0%	0.174
Deepness	79.3%	92.6%	0.078
Total regression	23.9%	4.7%	**< 0.001**
Relapse	0.0%	2.4%	0.552

Values in bold indicate statistical significance

evaluation and possible imaging investigation. A recent study advocated that the optimal time for referral or initiation of treatment was 1 month of age, which is much earlier than most

Table 4 Comparative analysis between twice- and thrice-daily dosage. Legend: *M* months, *IH* infantile hemangioma

	8/8 h $n = 97$	12/12 h $n = 13$	p
IH evolution			
Color	97.2%	90.0%	0.327
Diameter	98.6%	100.0%	0.880
Deepness	94.1%	83.3%	0.367
Regression			0.368
Partial	96.7%	90.9%	
Total	3.3%	9.1%	
Relapse	2.9%	0.0%	1.000
Adverse reactions	10.1%	8.3%	0.662
Mean treatment duration (M)	9.7 (±5.5)	10 (±2.9)	0.822

infants are typically referred to or evaluated by IH specialists, as seen in our sample. The reason behind this indication for such early referral was that IH growth was found to be non-linear, with an accelerated period of rapid growth between 5 and 7 weeks of age [14, 15].

Most IH are diagnosed clinically. Imaging studies and other investigations should only be performed in selected cases, such as diagnostic uncertainty (atypical appearance or growth), presence of five or more cutaneous IH (need to screen for hepatic IH), or if associated anatomic abnormalities are suspected [8, 10]. Doppler ultrasound should be the initial imaging test for diagnostic work-up and for hepatic HI screening and eventually to monitor progression and response to treatment [26, 27]. Magnetic resonance imaging (MRI) should be performed to address possible underlying structural abnormalities, namely, in infants at risk for PHACE or LUMBAR (lower body IH, urogenital anomalies/ulceration, myelopathy, bony deformities, arterial anomalies, renal anomalies) syndromes. These should be suspected in the presence of large segmental IH of the face/scalp and lumbosacral/perineal area, respectively [27–29]. As expected, imaging investigation was necessary in a minority of cases: Doppler ultrasound of the lesion was performed in 9.1%, abdominal ultrasound in 11.7% and MRI in 4.3%. In this last group, one infant had PHACE syndrome and was treated with both oral propranolol and laser, with partial regression of the segmental IH. Twenty (5.1%) infants had periorbital IH and were referred to ophthalmologic consultation to rule out amblyopia. Thyroid stimulating hormone screening was performed in two patients who had multifocal IH to rule out secondary hypothyroidism, which was not confirmed.

Decisions regarding intervention should be considered by a multidisciplinary team and based not only on risk stratification but also on the age and comorbidities of the child, location, classification and stage of evolution of the tumor, any actual or potential complications, and parental preferences [8, 10]. Approximately one-third of our sample underwent treatment with propranolol. Although there are no studies to date on the proportion of IH that are treated with propranolol, this percentage is probably overrated as a selection bias might have occurred since this study was carried out in a specialized tertiary center with inclusion of more complex and severe cases. Also, referral is more likely with larger or more visible IH; minor tumors are not usually referred. Despite this, it is known that the majority of infants who actually receive treatment do so to prevent uncontrolled growth leading to permanent disfigurement [8, 30]. This is in line with our results as the main indication for treatment was risk for esthetic compromise, present in almost half of our sample. Median age for propranolol initiation was four months, which shows that our hospital protocol follows the current literature that recommends initiation of treatment ideally between 5 weeks and 5 months of age, before the completion of the proliferative phase, in order to prevent poor outcomes [8, 15]. Patients that underwent treatment with propranolol before the age of 6 months tendentially had better outcomes, but this difference was not statistically significant. Therefore, we believe that treatment initiation after the recommended timings could still be beneficial in some patients and should be considered individually. The median duration of therapy was 9 months, which is also in agreement with the recommendations that therapy must be maintained for at least 6 months or until the end of the proliferative phase, which generally occurs by 1 year of age [8, 30]. The rationale for this recommendation is based on both efficacy and the risk of rebound after discontinuation. A large randomized controlled trial conducted in 2015 showed that a duration of 6 months of therapy was superior to 3 months [31]. Other study revealed that rebound growth may occur even after 6 months of therapy and that the greatest risk was in those in whom treatment had been discontinued prior to nine to 12 months of age [32]. Lack of response to treatment is rare and occurred in 0.8% of our patients, a percentage similar to what has been previously reported (0.9%) [33]. In turn, rebound growth after propranolol discontinuation is more common, being noted in 14–25% of children [22, 32, 34]. Segmental distribution and depth of the IH have been associated with an increased risk of relapse. Some children may need a second course of propranolol or topical timolol, but most cases do not require treatment [22]. Notably, in our sample, a rebound effect occurred in only six (5.1%) patients, three of which underwent a second cycle with propranolol and one underwent surgery. Our strategy, namely, treatment duration and gradual reduction, was probably a protective effect of rebound [35]. Among our patients, 8.3% experienced adverse effects. Similar percentages have been previously described in the literature (7–16%) [36–38]. Children treated with propranolol should be closely monitored and clinicians should educate caregivers about potential adverse effects. The most common are sleep disorders, somnolence, and irritability. Others less frequent but more worrisome include bronchospasm, hypotension, bradycardia, and hypoglycemia. To reduce the risk of hypoglycemia, propranolol should be given with or shortly after meals and the doses should be held at times of feeding refusal or vomiting. However, routine glucose screening is not indicated [8, 10]. Pretreatment electrocardiography (ECG) is controversial, once both hypotension and bradycardia tend to be mild and asymptomatic in children with no preexisting cardiac comorbidities. Although initially advocated by some, the most recent guidelines do not include routine ECG [8, 20]. However, in our current practice, all patients are evaluated by a pediatric cardiology and both ECG and echocardiogram are performed before starting propranolol to rule out the main contraindications to this therapy.

The results from the comparative analysis have shown that the group of patients that underwent treatment with propranolol had more risk factors and presented deeper and larger lesions. Total IH's regression was less frequent in this group, probably because the rate and extent of regression appear to be proportional to size, with larger lesions exhibiting longer periods of growth and involution [14, 39]. Initiation of propranolol as outpatient versus inpatient is changing as more evidence accumulates that cardiovascular and other acute toxicities rarely occur [8, 20]. Similarly, there are still no evidence-based recommendations on dosing frequency (twice daily versus thrice times daily), but both the Food and Drug Administration labeling and the European Medicine Evaluation Agency labeling are for twice-daily dosing [8]. Although we analyzed a short period of time after the application of our revised protocol (approximately 2 years), twice-daily dosage as well as inpatient initiation of propranolol had no significant differences in the incidence of adverse effects, duration of treatment, and lesion evolution. We consider that propranolol can be safely started on an outpatient basis for most infants and that twice daily frequency is equally safe and effective, in addition to being more comfortable for caregivers and increasing compliance.

Topic beta-blockers may be used in thin superficial IH and may also have a role in small ulcerated lesions and in preventing rebound growth after propranolol [40, 41]. Surgery and laser therapy are being used less frequently. Surgery could be indicated in IH that ulcerate, obstruct, or deform vital structures or involve esthetically sensitive areas and for residual skin changes, but only if medical therapy is thought to pose a greater risk and the resultant scar is likely to be acceptable [8, 10, 42]. In turn, the most accepted use of pulsed dye laser is the treatment of ulceration, post-involution erythema, and/or telangiectasias [43].

We acknowledge some important limitations to our study, including its retrospective nature, which limits data collection and the drawing of inferences from our results. Despite these limitations, to our knowledge, this is the largest European study assessing the management of IH and we reviewed information regarding a 12-year experience. Since it was carried out in a tertiary center, a selection bias is likely, probably neglecting smaller IH. Nevertheless, the vast majority of patients showed at least partial regression even in the absence of treatment.

Early detection of high-risk IH is paramount, requiring an increased awareness by pediatricians and general practitioners to identify potentially problematic lesions while in the early proliferation stage. Approximately one-third of the patients was treated with propranolol, a percentage that was probably overestimated due to the selection bias of more severe cases. In this series, no serious adverse effects were detected. Only 10.4% of patients underwent surgery and no complications were reported. Our hospital protocol, which was revised in 2020 based on the updated international literature, proved to be safe and feasible in an outpatient setting, reenforcing safety and efficacy of twice-daily dosage of propranolol.

Declarations

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