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ORIGINAL ARTICLE

Oral Propranolol for Treating Infantile Hemangiomas: A Case Series of 57 Patients

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Abstract

Introduction and objectives: Infantile hemangiomas (IH) are a frequent vascular tumor. In recent years, propranolol has emerged as an alternative in the treatment of IH. The objective of the present study was to evaluate the effectiveness of propranolol for the treatment of IH.

Materials and methods: Patients with IH requiring treatment were included. Cardiologic evaluation was made to every patient and electrocardiogram (ECG) and echocardiogram were done.

Oral propranolol was started in an ambulatory way at a dose of 2 mg/kg daily divided in two doses. At ten days all the patients were evaluated with a 24-h rhythm holter.

Evaluation of effectiveness: In clinical controls and by images IH were formally analyzed, without blindness. Response was categorized as complete response (CR), partial response (PR) and no response (NR).

Adverse events: Adverse events were registered in a special category of the formulary.

Results: 57 patients were included. Mean age was 9.7 months. There were 80.8% females. Mean duration of treatment was 7.3 months (1–24 months).

Efficacy: 50.6% had CR, 49.3% had PR. There were a 7% of adverse events. No differences in response rate exist according to age or location. No rhythm holter was altered at ten-day control.

Conclusion: Our study highlights the possibility of starting propranolol in an ambulatory way, establishes a dose of 2 mg/kg/day and confirms the security profile of the drug. We consider propranolol as a first line treatment for IH.

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PALABRAS CLAVE
Hemangiomas;
Propranolol;
tratamiento

Propranolol oral en el Tratamiento de los Hemangiomas de la Infancia: Serie de 57 pacientes

Resumen

Introducción y objetivos: Los hemangiomas de la infancia (HI) son un tumor vascular frecuente. En los últimos años, el propranolol ha demostrado ser una alternativa terapéutica para los HI. El objetivo del presente estudio fue evaluar la efectividad del propranolol para los HI.

Material y método: Lo pacientes que requirieron tratamiento de sus HI fueron incluidos. Se realizó evaluación por cardiología infantil en todos los pacientes. Se inició propranolol a una dosis de 2 mg/kg al día dividas en dos tomas. A los 10 días de tratamiento se realizó Holter de arritmias de 24 horas a todos los pacientes.

Evaluación de efectividad: se realizó formalmente en todos los controles clínicos y mediante iconografía, sin ciego. La respuesta se clasificó en respuesta complete (RC), respuesta parcial (RP) y no respuesta (NR). Los efectos adversos se registraron en un formulario especialmente diseñado.

Resultados: Se incluyeron 57 pacientes. La edad promedio al inicio fue de 9,7 meses. 80,8% fueron mujeres; la duración del tratamiento promedio fue de 7,3 meses (rango 1–24 meses).

Eficacia: se obtuvo 50,6% de RC y 49,3% de RP. No hubo diferencia al analizar la respuesta a tratamiento de acuerdo a la ubicación y a la edad. Hubo un 7% de eventos adversos sin haber ningún Holter alterado a los 10 días.

Conclusiones: Nuestro estudio destaca la posibilidad de iniciar propranolol de forma ambulatoria, establece una dosis de 2 mg/kg al día y confirma el perfil de seguridad del fármaco. Nosotros consideramos propranolol el fármaco de primea línea en el tratamiento de HI; en los casos en que sea necesario el tratamiento de estas lesiones.

Introduction

IH are the most common vascular tumors worldwide, affecting 5–10% of infants and up to 30% of premature babies.[1] They occur four times more frequently in females than in males.[2] Most of them are not present at birth and undergo rapid growing during infancy followed by an involution phase during the first few years.[3]

In the vast majority of patients with IH, treatment is not necessary and only strict follow-up is recommended; however, some patients with IH can be complicated and intervention is required.[4] These occur when they ulcerate, have massive growth, cause cosmetic impairment or disfigurement, and if they cause impact on normal function (e.g. periorificial hemangiomas).[5]

Medical treatments for IH include topical therapies with corticosteroids, imiquimod or timolol[6]; systemic therapies with oral or intralesional glucocorticoids; chemotherapeutic agents such as interferon and vincristine; surgery, and different kinds of laser therapies and the combination of these treatments.[4,5]

Propranolol, a non-selective β1 and β2 antagonist developed in 1950s by the Nobel Prize Sir James Black,[7] has shown to be effective in IH treatment. Since the serendipitous finding of Léauté-Labrèze et al. in 2008[8] many case-reports and case-series have arisen showing the usefulness of propranolol for treating IH.

Herein, we present a prospective case-series protocol of 57 IH patients treated with oral propranolol in an outpatient regimen.

Patients and methods

Hemangiomas needing treatment were defined as stated before and as commonly considered: those that may cause functional impairment or pain, ulcerated or at risk of being ulcerated, periorificial (e.g. ocular, nasal, earlobe, perioral), in the folds (e.g. axilla) and genitalia; and those who may cause scarring or disfigurement, as those in nasal tip or cheek.

This study was done between September 2008 and May 2011 at the Dermatology Department, Facultad de Medicina, Pontificia Universidad Católica de Chile.

Inclusion criteria: All infants who present at our dermatology department with IH who need treatment were offered to use propranolol. A complete history and physical examination, a basal ECG and cardiac echography (ECO) were done and all patients were sent to the pediatric cardiologist for cardiologic pass (this includes heart rate and blood pressure measurement and evaluation of exams: basal ECG and ECO). If this evaluation was normal, patients were included in the protocol. We did not request for basic biochemistry exams (glycemia, calcium, and others) unless patients were symptomatic or some disease was suspected.

Parents were told about this protocol and an instructive booklet with information about the medication was given. When there were diagnostic difficulties, an ultrasound of the involved area was done.

Exclusion criteria: Severe bradycardia, third grade atrioventricular blockade, or any known hypersensitivity to propranolol or cardiologic pass rejection.

Treatment protocol: All patients were received with the cardiologic pass and baseline pictures were taken. Propranolol was started in an outpatient regimen at a dose of 2 mg/kg daily divided in two doses orally. Since the first dose it was given at full dose and not gradually increased. Propranolol was reformulated as 10 mg per 1 mL suspension. A 24-h rhythm holter was done to all patients at 10 days of treatment, if normal treatment was continued. If altered, they were sent for a new cardiology-evaluation. In this 10-day control we did not control vital signs. While in treatment, they were controlled monthly without evaluation of vital signs or biochemical exams unless they were symptomatic. We did not measure thyroid hormones in large hemangiomas. Additionally, all parents were advised of bronchial obstructive diseases and the possibility of hypoglycemia with prolonged fasting due to inherent risks of propranolol.

Patients were controlled monthly without evaluation of vital signs or glycemia.

In patients with proliferating lesions (infants under the age of 12 months) propranolol was continued until the theoretic conclusion of this proliferative phase until at least the age of 12 months. Patients who began treatment when older than 12 months took propanolol for at least 6 months. If lesions were still responding, we continued the medication. If lesions were no longer responding when the patient reached an age target, we continued treatment with the drug for 1 additional month and then discontinued it if response was not evident. If after withdrawal of propranolol lesions rebounded, we started again with the same previous scheme until achieving the same previous clinical response and then weaned as stated in the treatment protocol.

Propranolol was weaned gradually at the end of the treatment in one month to 1 mg/kg daily, and then was completely stopped. If cosmetic sequels were evident at the end of the treatment, like redundant skin (that was not corrected by propranolol), patients were sent for Plastic Surgeon evaluation for surgical correction. These evaluations were not registered in this study.

Evaluation of effectiveness: All patients had baseline pictures taken before the initiation of propranolol and monthly in every control. IH were formally analyzed by images and in monthly follow-ups, without blindness, by the same investigators of the study and a global score, based on color, volume, size and consistency was entered as follows:

1. CR: complete resolution of the IH. Residual lesions (telangiectasias and redundant tissue) were allowed and also considered CR.
2. PR: reduction in size, change in color or consistency without being a CR.
3. NR: any change at all when compared to baseline photographs or continue growing while in treatment.

This evaluation was done the last day the patients were followed-up, independently of treatment time or if treatment was already finished. We did this to evaluate the final outcome of propranolol as stated in our primary objective.

Others: Patients with ocular or periocular hemangiomas were evaluated by an ophthalmologist; if needed, an ophthalmology follow-up was indicated.

Adverse events: Adverse events were registered in a special category of the formulary. Every adverse event was consigned there only if they were symptomatic, because we did not control vital signs in follow-ups. Hypotension, bradycardia, bronchial obstruction and hypoglycemia were specially emphasized.

Informed consent: Parents of every patient signed a two-copy written informed consent included in the informative booklet. No parents rejected the use of propranolol after detailed information of the drug safety was given.

Statistical analysis: It was done using MINITAB® 15 (LEAD Technologies, Inc.). Values were analyzed using Chi-square test for age correlation and Pearson Chi-square test for analysis of location. A *p*-value was considered statistically significant when it was <0.05 (95%).

Results

57 patients were compatible with inclusion criteria and started oral propranolol.

Baseline characteristics (Table 1)

Mean age at the beginning of the study was 9.7 months (standard deviation 12.05, minimum 2 months, and maximum 79 months). There were 80.8% female and 19.2% male patients in the study.

There were 77 hemangiomas, mean number of hemangiomas per patient was 1.3 (standard deviation 0.9). 9 of 57 patients had more than one IH; two patients had five hemangiomas. 87.7% of patients had focal hemangiomas and 5.2% had multiple hemangiomas (defined as more than five IH and visceral hemangiomas).

7% of patients had segmentary IH; of them, 3 patients were on trigeminal branches distribution (patients 5, 25 and 48) that prompted a study for PHACE syndrome. The study was done in an ambulatory way with magnetic resonance of brain and neck with angiography. ECO was not done because it was requested in the preliminary study. They were also evaluated by an ophthalmologist. In the three of them the study was normal and could use propranolol.

Hemangiomas by site were as follows: 58 of 77 hemangiomas (75.4%) were on head and neck (twelve periocular, ten on lips, nine on cheeks, six were on nasal tip, five on the scalp, four on earlobe, two on parotid region, two on neck, one on mandible, one on filtrum, one interciliary, one segmentary on trigeminal branch V1, V2 and V3, one preauricular, one in nasal dorsum, one on glabella and one on chin region). Two were on axilla; five were on shoulder; forearm or hand; six were on lower limbs; five were on trunk and there was one genitalia involving hemangioma. There were three patients with visceral hemangiomas; all of them were multiple hepatic hemangiomas and were not considered in the total number of IH.

Patients with ocular or periocular involvement were evaluated by a pediatric ophthalmologist. All the evaluations were normal and a follow-up was scheduled in 6 months. Patient 25 had almost complete occlusion that led to the development of amblyopia. She started treatment with an occlusive dressing 4 h daily to the healthy eye and a monthly control was started. She improved notably with propranolol. This patient is still on follow-up because of persistent amblyopia.

Table 1 Patient's characteristics and response to propranolol. IC stands for injectable corticosteroids. ASD: atrial septal defect.

Patient	Sex	Type	Location	Number	Age at beginning of treatment (in months)	Duration of treatment (in months)
1	F	Focal	Axilla	1	11	12
2	F	Focal	Nasal tip	1	2	8
3	M	Hemangiomatosis	Hand, scalp, neck, hepatic hemangiomas	3	5	9
4	F	Focal	Earlobe, dorsal, leg	3	18	6
5	F	Segmentary	Earlobe, lip, mentonian	3	33	3
6	F	Focal	Cheek	1	7	7
7	F	Focal	Nasal tip	1	2	5
8	F	Focal	Superior lip	1	2	9
9	F	Focal	Cheek	1	18	6
10	F	Focal	Frontal	1	6	1
11	F	Focal	Mandibular with otic compromise, genital	2	12	10
12	M	Focal	Periocular	1	2	3
13	M	Focal	Nasal tip	1	31	1
14	F	Focal	Filtrum	1	2	12
15	F	Focal	Cheek	1	13	16
16	F	Focal	Perioral	1	2	4
17	F	Focal	Nasal tip	1	11	14
18	F	Focal	Periocular	1	3	4
19	F	Focal	Cheek	1	4	5
20	F	Focal	Periocular	1	3	7
21	F	Focal	Inferior lip (mucosa)	1	2	12
22	F	Focal	Nasal tip	1	3	2
23	F	Segmentary	Forearm	1	2	12
24	M	Focal	Neck	1	8	3
25	F	Segmentary	Temporoparietal-palpebral	1	2	5
26	F	Focal	Palpebral, shoulder, scalp	3	2	12
27	F	Focal	Cheek	1	3	10
28	F	Focal	Glabella	1	6	5
29	F	Focal	Intraparotid, shoulder, feet, buttock, knee	5	21	4
30	F	Focal	Sores (not slimy)	1	21	7
31	F	Focal	Nasal tip	1	7	24
32	F	Focal	Earlobe, periocular (internal angle)	2	11	7
33	F	Focal	Superior lip	1	79	6
34	M	Focal	Nasal dosum	1	2	8
35	M	Focal	Superior lip (mucosa)	1	4	8
36	F	Focal	Interciliar	1	11	3
37	M	Focal	Nasal tip	1	5	6
38	F	Focal	Abdominal	1	4	1
39	F	Focal	Cheek	1	15	12
40	F	Focal	Cheek	1	5	4
41	F	Focal	Cheek	1	21	3
42	F	Focal	Inferior lip (no mucosa)	1	4	16
43	F	Focal	Pre auricular (external auricular canal and parotid comprise)	1	15	13
44	M	Focal	Inferior lip (gingiva compromise)	1	2	2
45	M	Hemangiomatosis	Cheek/infrapalpebral, axilla, back (2)/multiple hepatic hemangiomas	5	6	2
46	F	Focal	Inferior lip (gingiva compromise)	1	25	5
47	F	Focal	Palpebral	1	2	9
48	F	Segmentary	Earlobe, V1, V2, V3 and parotid compromise	1	12	15
49	F	Focal	Periocular	1	5	7
50	F	Focal	Cheek and inferior eyelid	1	2	5

Table 1 (*Continued*)

Patient	Sex	Type	Location	Number	Age at beginning of treatment (in months)	Duration of treatment (in months)
51	M	Focal	Buttock	1	5	5
52	F	Focal	Palpebral	1	8	10
53	F	Focal	Superior lip (no mucosa)	1	9	13
54	F	Focal	Palpebral	1	15	12
55	F	Focal	Glabella	1	17	5
56	F	Focal	Pectoral	1	2	3
57	M	Hemangiomatosis	Periocular, hand, leg, hepatic hemangiomas	3	3	2

Patient	Sex	Adverse events	Response	Lost of follow-up	Rebound	Previous treatment	Others
1	F	No	Partial	No	No	No	No
2	F	No	Complete	No	No	No	No
3	M	Rash	Complete	No	No	No	No
4	F	No	Partial	No	No	I.C.	No
5	F	No	Partial	No	No	I.C.	No
6	F	No	Complete	No	No	No	No
7	F	No	Partial	No	No	No	No
8	F	No	Partial	No	No	No	No
9	F	No	Partial	No	No	I.C.	No
10	F	No	Partial	No	No	No	No
11	F	No	Complete	No	No	I.C.	No
12	M	Overdose	Partial	No	No	No	No
13	M	No	Partial	Yes	No	I.C.	No
14	F	No	Complete	No	No	No	No
15	F	No	Complete	Yes	No	No	No
16	F	No	Complete	No	No	No	No
17	F	No	Complete	No	Yes	No	No
18	F	No	Partial	No	No	No	No
19	F	No	Partial	No	No	No	No
20	F	No	Partial	No	No	No	No
21	F	No	Partial	No	No	No	No
22	F	No	Complete	Yes	No	No	No
23	F	No	Complete	No	No	No	No
24	M	No	Partial	No	No	No	No
25	F	No	Complete	No	No	No	No
26	F	No	Complete	No	No	No	Left hemiblock
27	F	No	Complete	No	Yes	No	No
28	F	No	Complete	No	Yes	No	Persistent ductus arteriosus
29	F	No	Complete	No	No	No	No
30	F	No	Partial	No	No	I.C.	No
31	F	No	Partial	No	Yes	I.C.	No
32	F	No	Complete	No	No	No	Osteogenesis imperfecta
33	F	No	Partial	No	No	I.C.	No
34	M	Sudoration	Partial	No	No	No	No
35	M	No	Complete	No	No	No	Ventricular extrasystole
36	F	No	Complete	Yes	No	No	No
37	M	No	Complete	Yes	No	No	No
38	F	No	Partial	Yes	No	No	No
39	F	No	Complete	No	No	No	No
40	F	No	Partial	No	No	No	ASD/apneas
41	F	No	Complete	Yes	No	No	No
42	F	No	Partial	No	No	No	No
43	F	No	Partial	No	Yes	I.C.	No
44	M	No	Partial	No	No	No	No

Table 1 (*Continued*)

Patient	Sex	Adverse events	Response	Lost of follow-up	Rebound	Previous treatment	Others
45	M	Sleepiness	Partial	Yes	No	No	Persistent ductus and bronchopulmonar dysplasia
46	F	No	Complete	No	No	No	No
47	F	No	Complete	No	No	No	No
48	F	No	Partial	No	Yes	No	No
49	F	No	Partial	No	No	No	No
50	F	No	Complete	No	No	No	No
51	M	No	Partial	No	No	No	No
52	F	No	Complete	No	No	No	No
53	F	No	Complete	No	No	No	No
54	F	No	Complete	No	Yes	No	No
55	F	No	Complete	No	No	No	No
56	F	No	Complete	No	No	No	Persistent ductus arteriosus
57	M	No	Partial	No	No	No	No

Four patients had mucosal involvement. We did not consider mucosal involvement in one patient who had involvement of the ear canal because his IH did not compromise tympanic mucosa. Three patients had parotid involvement.

At the beginning four patients had ulcerated IH. Patients 14, 25 and 45 started propranolol and mupirocin 2% twice daily for 7 days and at 1-month follow-up ulceration was not evident and completely healed. Patient 51 was treated with topical chloramphenicol and 4 sessions of pulse-dye laser in another center with PR and an incomplete healing of the ulceration. Propranolol was started and at one-month follow-up it was completely healed.

Nine patients have had previous treatments, of them; all used intralesional corticosteroids (IC). In five of them parents did not remember the drug or dose used and they were treated in other center but all have PR or NR. Patient

4 used 10 mg triamcinolone monthly for 4 months since 3 months with PR; patient 9 used 10 mg triamcinolone monthly for 5 months since 9 months with PR. Patients 11 and 13 both used betamethasone (dose not reported) monthly for 6 months since 3 months of age with NR. Patient 30 used 10 mg triamcinolone monthly for 3 months since 5 months with PR.

Efficacy

Patients were evaluated monthly with the protocol stated earlier; some of them had finished their treatment while others were still on treatment when this paper was written. We considered the last visit for evaluating effectiveness and as the final outcome. 50.6% (39/77) of IH had CR evaluated by the three investigators. 49.3% (38/77) had PR, and 0/77 IH

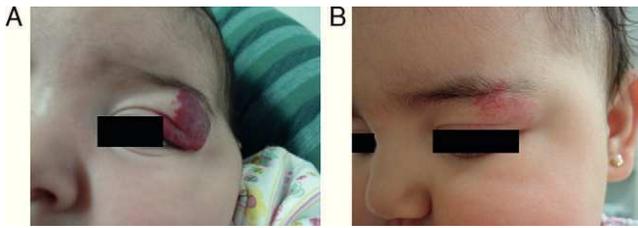**Figure 1**   Patient number 3. (A) Start at two-months and (B) one-year follow-up.

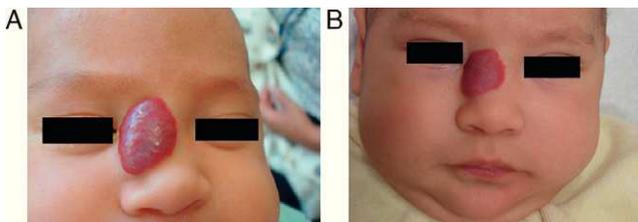**Figure 2**   Patient number 26. (A) Start at two months and (B) fifth-month follow-up.

Figure 3   Patient number 34. (A) Start at two-months and (B) second-month follow-up.

had NR. Additionally, no IH continued growing while in treatment (Figs. 1–5). At one-month follow-up, one patient with hepatic hemangiomas had an abdominal ultrasound showing decrease in size (from 1.6 cm to 1 cm).

Treatment duration had a mean of 7.3 months (standard deviation 4.6) with a minimum of 1 and a maximum of 24 months. Nine patients were lost at follow-up so definitive analysis could not be made and the efficacy of response was that of their last control.

Response rate underwent a subgroup analysis. In those 7 months or older CR rate was 57.1% and in those 6 months or younger it was 45%. These differences were not statistically significant (p-value: 0.29). Also, we did not find any statistically significant differences according to IH location (p-value: 0.55) or type (focal or segmentary; p-value: 0.93) (Fig. 6).

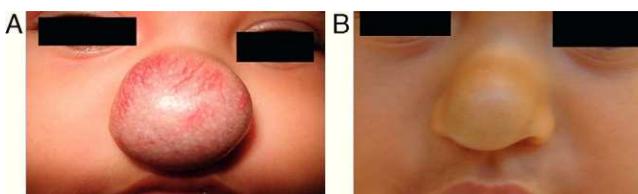When propranolol was withdrawn 7.7% of IH rebounded. Patient 17 was treated for six months and after 3 months

Figure 4   Patient number 37. (A) Start at five months and (B) sixth-month follow-up.

Figure 5   Patient number 42. (A) Start at 4 months and (B) ninth-month follow-up.

without propranolol the lesion rebounded; she was then treated for an additional period of 8 months and after 4 months of follow-up since withdrawal, the IH was still in CR. Patient 28 used propranolol for 5 months and had a little rebound after 1 month who did not require restart of treatment.

Patient 31 was treated for 7 months. The IH grew again after 3 months without propranolol and was treated again for 12 months and then withdrawn. After 15 days it rebounded again so propranolol was held for a total of 24 months. Patient 43 was treated for 8 months; then she was 4 months without treatment and her IH rebounded so propranolol was restarted for 5 additional months.

Patient 48 had a parotid focal IH that was treated for 10 months and treatment was suspended; after 5 months without treatment the IH reappeared so propranolol was restarted for 5 months and is still in treatment. Patient 54 completed 12 months of treatment; after 2 months without the drug parents referred a rebound but propranolol was not restarted.

In all these cases when propranolol was restarted the response rate, which was reached within the prior treatment protocol, was recovered. The drug was then stopped as stated in the protocol in 'Patients and methods' section.

Adverse events

No 24-h rhythm holter was altered at ten-day follow-up.

There were 4 adverse events in our register (7% of patients). One patient with sweating (glycemia 91 mg/dL; no control of vital signs) resolved spontaneously. One patient was with somnolence at third day of treatment: he consulted at emergency room with normal glycemia (104 mg/dL), normal blood pressure (120/60 mmHg) and with normal heart rate (140 beats/min). He was sent home and also resolved spontaneously. One patient had a skin rash (that responded to anti-histamines).

Patient 12 had an overdose because of dose mistake by his mother (ten times the dose). She gave 0.3 mL instead of 3 mL (20 mg/kg). In the emergency room he was restless, euphoric and with insomnia. Blood pressure, heart rate and glycemia were normal. This last patient needed 24 h hospitalization in an intensive care unit for motorization and did not contraindicate the use of propranolol.

15/57 (26.3%) of the patients had lower respiratory tract infection (bronchitis) that were highly probable in the context of a viral infection and prompted an eventual withdrawal of the drug. They were not considered an adverse event of the drug in any patient.

Others

7/57 patients had comorbidities known by the parents before the initiation of treatment that were not influenced nor contraindicated propranolol: one patient had *osteogenesis imperfecta*, one patient had ventricular extra-systole while in treatment, one patient had left bundle hemi-block, one patient had atrial septal defect and apneas, three patients had patent ductus arteriosus (one also had bronchopulmonar dysplasia). Treatment did not influence any of
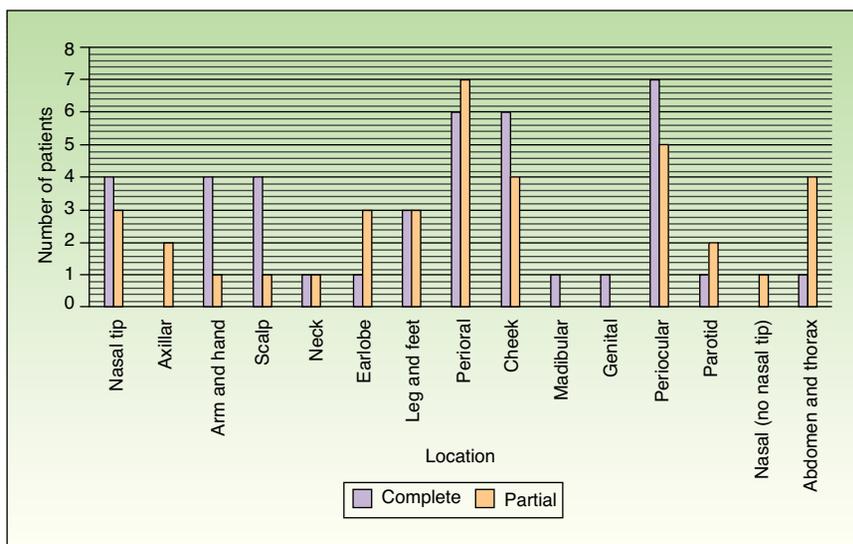
Figure 6   Response rate of hemangiomas according to location (Pearson-χ^2; $p = 0.559$).

these patients and follow-up was done similar to patients without comorbidities, after the primary evaluation with a cardiologist.

Discussion

We have presented 57 patients with IH treated with propranolol; to our knowledge, one of the largest series published in English and Spanish literature.[5,9–15] Since the extraordinary response of IH published in 2008,[8] our group started a protocol for propranolol in treating IH.

In our series, we found a 50.6% of CR, which is a little bit lower than published elsewhere[5,9–16] but similar to the 66.6% of CR reported by Bernabeu-Wittel et al.[13] Sans et al. found a 100% of response on 32 children with IH.[11] Buckmiller et al.[5] reported that 97% of their 32 patients had any response to propranolol. Bagazgoitia et al. found an average reduction of IH of 60% evaluated as a score considering size and color as the main features.[12]

These differences could be explained because we considered CR as the main outcome, which is a more standardized way for the evaluation and interpretation of the response rate of IH to propranolol than ''any response'' used in some reports. If we had considered the final outcome as ''any response'', we would have found a response rate of 100%, with any patient falling into the category of NR.

The oldest infant treated with propranolol in the literature is also in our series: a 79-month-old female who was previously treated with intralesional corticosteroids with PR; she completed 6 months of treatment with propranolol with good response.

Under our results, it seems that there is no difference in propranolol response in infants younger or older than six months of age when starting the drug. This was also found in other series.[12,13] Also, we did not find any statistically significant association between IH location or type (focal or segmentary) and response rate; however the number of patients treated in the location groups is low for a definite statistical analysis; however, this results are similar to other IH series[12,13] and are in concordance with our feelings that

IH respond to propranolol in any location or any type of IH.[12] We cannot deny that differences according to hemangiomas location or type may be found if larger series analyze this association in future studies.

An additional feature of our study is that seven patients had cardiologic and respiratory comorbidities prior to initiation of treatment that did not contraindicate propranolol and did not produce any symptomatic adverse events on patients. This is a new insight on the use and safety profile of this drug in patients with cardiopulmonary comorbidities without any adverse events and without the need for strict monitoring in addition to the first cardiologic visit. This opens a window of possibilities to children that would be automatically excluded of the opportunity to receive propranolol because of these cardio-respiratory comorbidities. We encourage an evaluation with a pediatric cardiologist to balance the risk–benefit ratio in these patients.

Recently some case series of ulcerated hemangiomas responding to propranolol have been published,[12,14–16] however, variable results exist.[13] We found four patients with ulcerated IH, and all of them healed in the first month of treatment. Also, one patient had NR to multiple treatments before the start of propranolol. This is a very important feature because ulcerated hemangiomas are often difficult to treat, they are painful, they can prompt to locally or systemic infections and cause scars and disfiguration and therefore always require treatment; making propranolol a good alternative for ulcerated IH as commented by other authors.[12–16]

We only found four adverse events; one was a serious adverse event but it was because the patient's parents did not understand our indications so they gave him ten times the dose. He needed 24 h-transient hospitalization with cardiorespiratory monitoring in an intensive-care unit but he did not have bradycardia, hypotension or hypoglycemia; so no serious adverse events were found if propranolol is well administered without overdosing. The others were just mild adverse events. Similar adverse events profiles have been reported by Manunza et al.[9] and commented by other authors.[17]

Other authors have observed more severe adverse events; de Graaf et al.[18] found two patients with hypoglycemia. One of them had adrenal insufficiency secondary to a sudden withdrawal of corticosteroids and the other had prolonged fasting when presenting it. They also found bronchial hyperresponsiveness, hypotension, restless sleep, constipation and cold extremities. Others had shown similar adverse events: increased sleepiness, gastro-esophageal reflux, allergic rash and respiratory virus exacerbation.[5] Other adverse events reported are masking of the initial clinical signs of cardiac failure and diminish of cardiac performance; lessening clinical features of hypoglycemia[19] and hypoglycemia[20] particularly in patients younger than 1 year,[21] hyperkalemia, maybe mediated by tumoral lysis mechanism,[22] bradycardia,[23] diarrhea,[24] and probable cerebral hypoperfusion and theoretical brain tissue infarction in patients with PHACES syndrome[23]; this hypothesis is not accepted by all and no cerebral infarction has been found in propranolol treated patients.[9] We did not find any patient with nightmares or agitated dreams, a feature reported in 14% of patients by other authors.[12]

Propranolol has also been successful for hepatic hemangiomas[25] and airway IH.[26] Three patients of our series had hepatic hemangiomas, two of them were asymptomatic and we did not perform hepatic images after treatment. One patient had a control abdominal ultrasound showing a decrease in size of hepatic hemangiomas.

One flaw of our study is the absence of a control group to compare outcomes; another weakness is the absence of an objective way to measure the improvement of IH; we tried to make an objective measurement but it is not as objective as it should be; we intended to by-pass this with an independent evaluation by three investigators of the study (MSZ, CN, AA) attempting to isolate the ''complete response''[13] instead of the previously reported ''any response''. We cannot fully ensure that some IH classified as ''complete response'' are really a ''partial response''.

This study is different from others published elsewhere because we started propranolol in an ambulatory way, with an initial dose of 2 mg/kg/day without making an escalating dose, and without strict monitoring of vital signs in the first hours or in every control. We found this simpler scheme safe and without any serious adverse events on 57 patients and almost three years of experience. Patients were given the treatment (after cardiologic pass) and controlled 10 days later with a 24-h rhythm holter; then they were cited every month. As none of the rhythm holters made to our patients were abnormal; we suggest that this costly and troublesome exam should not be done.

We neither measured serum chemistry nor controlled vital signs in monthly follow-ups. We only referred patients to the emergency department if they were symptomatic for evaluation of heart rate, blood pressure, pulse oximetry and glycemia. Doing this, we enhanced specificity but sacrifice sensitivity. We also think that these measures may lower costs to the health systems and to the patients.

In view of our results, and what is published elsewhere about the safety profile of propranolol and beta-blockers in children,[27] we postulate that basal echocardiogram and 24-h rhythm holter at 10 days should not be done and we disagree with starting propranolol in an inpatient way. We also encourage an initial cardiologic visit for a complete cardiologic physical examination; our group suggests these procedures as being sufficient to start the drug in an outpatient way, as outlined by López Gutiérrez.[28] Parents must be reaffirmed about the dosage of propranolol because we found that the only severe adverse event was originated in a propranolol-overdose. We prescribe the drug two times per day instead of three times per day to increase adherence to treatment,[29,30] an important issue to asses when giving any treatment. We believe that less doses is a better compliance.

We agree with some authors[31,32] that propranolol must be the first-line treatment for IH because it is highly efficient and with a low adverse-events profile. We also suggest that the dose of propranolol for treating IH is 2 mg/kg/day divided in two daily doses[17] to increase adherence to treatment.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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