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Long-Term Treatment with Oral Propranolol Reduces Relapses of Infantile Hemangiomas

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Abstract: **Oral propranolol (OP) has been shown to be effective in the treatment of complicated infantile hemangiomas (IHs), but optimal treatment duration to avoid relapses after stopping OP treatment has not been established. The objective of this study was to compare the frequency of relapses in long-term OP treatment with that of short-term OP treatment. This was a retrospective cohort study of 30 patients with complicated IHs who received treatment with OP. Patients were divided into two groups: OP treatment of 8 months or less and OP treatment of longer than 8 months. OP was started at 1 mg/kg/day in three doses every 8 hours for 1 week and increased to 1.5 to 4 mg/kg/day afterward. Ultrasound was used to objectively measure the response to treatment. Clinical and ultrasound assessment showed a decrease in IH size and resolution of complications in all patients (n = 30). In the short-term group (n = 10), nine patients (90%) relapsed after stopping treatment. In the long-term group (n = 20), the duration of treatment was 12 months in all patients, and only 1 patient out of the 20 treated (5%) showed relapse 2 months after finishing the full treatment (odds ratio = 18, 95% confidence interval 2.6, 123, $p < 0.001$. Twelve months of treatment of IH with OP is associated with a significantly lower rate of relapse than with shorter treatment.**

Infantile hemangiomas (IHs) exhibit a proliferative phase followed by stabilization and involution (1). Approximately 10% of IHs require intervention during the proliferative phase. Oral propranolol (OP) is an effective treatment for complicated IHs (1). Its effectiveness, adverse effects, dose, and treatment monitoring have been widely described (1–8), but optimal treatment duration to avoid relapses has not been addressed.

The purpose of this study was to compare the frequency of relapses with long-term versus short-term OP treatment based on an analysis of a retrospective

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cohort study of patients with complicated IHs treated with OP. In addition to the traditional clinical follow-up, ultrasound images were used as an objective assessment of treatment efficacy.

METHODS

This retrospective cohort study included 30 patients with complicated IHs treated with OP. Patients were treated at our Vascular Anomalies Center from March 2009 to August 2011 and received no treatment other than OP. Approval for publication was obtained from the institutional review board of our Research Ethics Committee.

We collected data from all patients younger than 18 months old who had been treated at our Vascular Anomalies Center with OP because of functional impairment, ulceration, or disfigurement caused by an IH.

Patients were treated in an outpatient setting, except for premature infants, who were admitted. A pediatric dermatologist and a pediatric cardiologist monitored all patients before and during treatment. Examinations included electrocardiogram, heart rate, blood pressure, and echocardiography at initial evaluation and then monthly electrocardiogram, heart rate, and blood pressure. Serum electrolytes, liver functions tests, and blood glucose levels were also determined before treatment and monthly thereafter. Objective response to treatment was assessed according to ultrasound color Doppler evaluation of IH thickness and vessel density before starting treatment and then monthly. In 85% of cases, the same physician (FD) performed ultrasound examinations; an Esaotte My Lab 70 with a linear 9- to 18-MHz transducer was used. Color Doppler ultrasound images were also obtained to estimate vessel density.

OP (propranolol hydrochloride) was started at 1 mg/kg/day in three divided doses every 8 hours for 1 week and increased to 1.5 to 4 mg/kg/day afterward. The dosage increases were based on clinical response and ultrasound findings. To provide the right dose, 10-mg tablets of propranolol were administered complete or were divided in halves or quarters if necessary, crushed and resuspended in a few milliliters of water or milk. Caregivers prepared the medication, which was administered after feeding to avoid hypoglycemia.

During the first phase of the study, patients were treated with OP for 3 to 8 months (short treatment). Treatment duration was based on apparent response to treatment (visible reduction of the hemangioma). Follow-up of these patients showed a high rate of relapse, so based on these initial results, all new patients entering the study were treated for 12 months (long treatment). The treatment modalities (long or short) were sequential, and there was no preestablished randomization of patients treated for the short or longer time. Although treatment allocation was not randomized, no potential confounders related to outcomes were identified between the two treatment groups, such as type of IH, OP dosage, or age at treatment initiation.

The patients were followed for at least 12 months after discontinuing the treatment. Relapse was defined as recurrence of the complication that led to the indication to treat or as an increase in IH thickness of more than 50% from the last measured point. The patients who received the short treatment were re-treated for a longer time, but the results after their re-treatment are not included in this study.

Descriptive statistics and parametric and nonparametric tests were used to summarize and compare characteristics in the short and long treatment groups. Time to relapse after treatment discontinuation was analyzed using the Kaplan–Meier method and the long-rank test (Fig. 1). The difference in the relapse rate between the two groups was reported as the odds ratio (OR) and corresponding 95% confidence interval (CI).

RESULTS

Table 1 summarizes patient age, type and location of the IH, the reason for treatment, and outcomes. Age at initiation of treatment was between 2 and 14 months in the short treatment group and between 0.5 and 6 months in the long treatment group. Figure 2 shows an ulcerated IH in patient 7 at the beginning of treatment.

The OP dosage was 1.5 to 2 mg/kg/day in all patients, except for two patients in the long treatment group—patients 17 and 18, premature twins who did not respond to the medication until they received 4 mg/kg/day.

Table 2 describes the ultrasound findings for the 30 patients in the study. On average, a 12% decrease in maximal thickness of the IH was observed at 7 days of treatment, 38% at 1 month, 59% at 4 months, and 74% at 12 months. In ulcerated IHs, healing of the ulceration occurred after an average period of 28.5 days (range 7–45 days). At the end of the treatment, 4 (13.3%) patients showed a reduction in IH thickness of less than 50%, 14 (46.6%) a reduction of 50% to 75%, and 12 (40%) a reduction of more than 75%.

Immediately after treatment was stopped there was a slight darkening of the lesions, with no significant

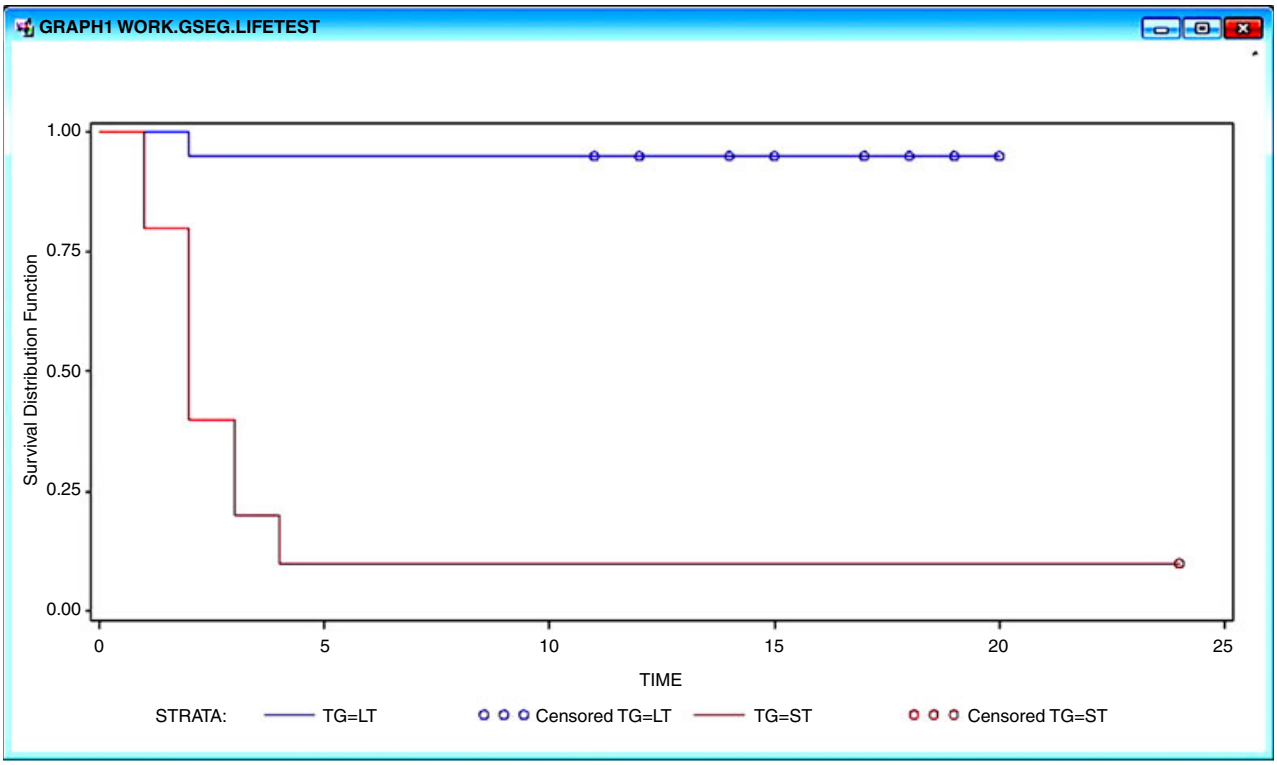

Figure 1. Time to event analysis; long-range test < 0.001.

increase in the thickness of the IH. Then, in most cases the IH continued to improve. In all patients, clinical and ultrasound assessment showed a decrease in IH volume and resolution of complications during the OP treatment period, including healing of ulcers, recovery of vital functions or prevention of functional impairment, and aesthetic improvement of the deformity. Figure 3 shows the decrease in volume and complete healing of ulceration after 4 months of IH treatment in patient 7.

Table 3 provides detailed information about the duration of OP treatment and follow-up measurements for each of the 30 patients in the study. The duration of therapy for the short treatment group was from 3 to 8 months (average 4.5 mos). IH relapse was observed within 4 months (range 0.5–4 mos) after stopping treatment in 9 of the 10 (90%) patients in this group. Figure 4 shows the ulceration recurrence during the onset of relapse in patient 7. OP was reinitiated in all patients with relapse with the exception of two patients.

The duration of treatment for the long treatment group (patients 11–30) was from 11 to 13 months (average 11.8 mos), and only 1 patient (patient 16) of the 20 treated (5%) showed relapse 2 months after finishing OP treatment. At the beginning of treatment, this patient presented a small (3 cm × 3 cm) but disfiguring ulcerated mixed IH on the left cheek. The relapse consisted of a 50% increase in thickness from the results achieved at the end of treatment; it was disfiguring, but without ulceration. The period of time for relapse was less than 6 months in both cases (Fig. 1).

Comparison of the results between groups showed that 12 months of treatment is associated with a significantly lower rate of relapse (5%) than treatment of less than 8 months (95%) (OR = 18, 95% CI 2.6, 123).

None of the patients had severe side effects such as bradycardia or hypoglycemia. Nine patients (30%) had minor side effects, including mild bronchospasm due to bronchiolitis in three, somnolence in two, cold hands and feet in three, and a mild increase in the levels of transaminases that normalized once the treatment was completed in one.

DISCUSSION

Our experience treating 30 patients with complicated IH supports other reports indicating that OP is a remarkably effective and well-tolerated drug for treating this condition (1–7), but reports on relapse of IH in patients treated with OP have been scarce,

TABLE 1. *Patient Age, Type and Location of IH, Reason for Treatment, and Outcome*

Oral propranolol treatment	Patient	Age at beginning of treatment (months)	IH type	IH location	Reason for treatment	Outcome
Short term	1	5	Deep	Periocular	Astigmatism	Improvement in astigmatism
	2	2	Combined	Genital	Urinary tract obstruction	IH volume decrease
	3	6	Deep	Forehead	Disfigurement	IH volume decrease
	4	6	Combined	Side	Ulcerated	Complete healing
	5	12	Combined	Scalp	Ulcerated	Complete healing
	6	7	Deep	Periocular	Disfigurement	IH volume decrease
	7	2	Combined	Genital	Ulcerated	Complete healing
	8	14	Combined	Periocular	Ulcerated	Complete healing
	9	2	Deep	Nasal	Disfigurement	IH volume decrease
	10	6	Deep	Lower lip	Disfigurement	Complete healing
Long term	11	6	Combined	Lower lip	Disfigurement	IH volume decrease
	12	6	Superficial and hepatic IH	Multiple cutaneous and hepatic IH	Multiple hepatic hemangiomas	IH volume decrease
	13	2	Combined	Upper lip and nasal	Disfigurement	Complete healing
	14	6	Deep	Periocular	Disfigurement	Improvement in palpebral occlusion
	15	6	Combined	Hip	Ulcerated	Complete healing
	16	5	Combined	Cheek	Ulcerated	Complete healing
	17	0.5	Combined	Lower lip	Ulcerated	Complete healing
	18	0.5	Combined	Nasal	Ulcerated	Complete healing
	19	1	Deep	Nasal	Disfigurement	IH volume decrease
	20	2	Combined	Lower lip	Ulcerated	Complete healing
	21	5	Deep	Cheek	Disfigurement and parotid gland	IH volume decrease
	22	1	Deep	Nasal	Disfigurement	IH volume decrease
	23	5	Combined	Cheek	Disfigurement	IH volume decrease
	24	2	Deep	Lower lip	Disfigurement	IH volume decrease
	25	2	Deep	Submaxilar	Disfigurement and parotid gland	IH volume decrease
	26	2	Deep	Nasal	Disfigurement	IH volume decrease
	27	2	Combined	Periocular	Palpebral occlusion	Improvement in palpebral occlusion
	28	5	Combined	Neck	Ulcerated	Complete healing
	29	3	Deep	Submaxilar	Disfigurement and parotid gland	Complete healing
	30	6	Combined	Periocular, nasal, upper lip	Disfigurement	IH volume decrease

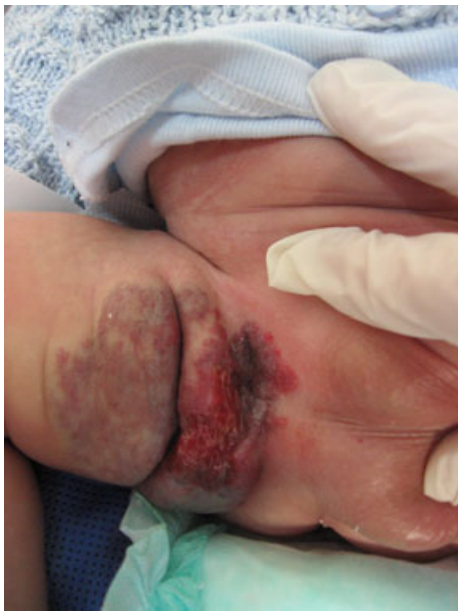

Figure 2. Patient 7. Genital ulcerated mixed IH at the beginning of OP treatment.

and thus the length of the treatment or treatment dosage to avoid relapse has not been definitively established (8).

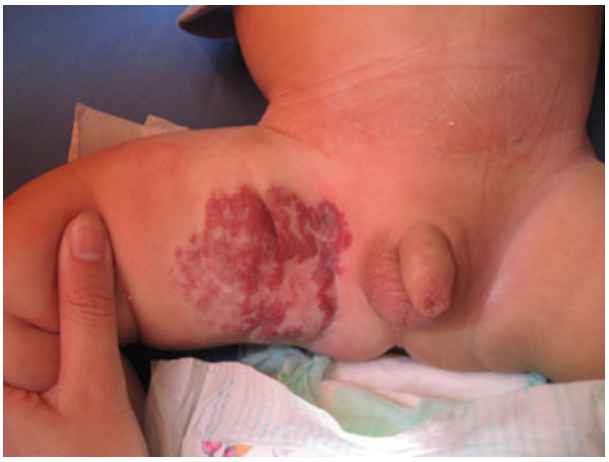

Figure 3. Patient 7. Decrease of IH thickness and vascularization, with complete healing of ulceration after 4 months of OP treatment.

Our study showed that patients treated for 3 to 8 months had a relapse rate of 90%, whereas patients treated for longer than 8 months had a much lower relapse rate (5%). It is likely that the longer duration of the proliferative phase in deep and segmental IHs (9) is the main reason for this feature, although other

TABLE 2. *Ultrasound Findings of Diminishment of IH Thickness*

Oral propranolol treatment	Patient	7 days of treatment (%)	1 month of treatment (%)	4 months of treatment (%)	12 months of treatment (%)
Short term	1	16.6	75	85.8	85.8
	2	16	38.1	56.5	67.1
	3	13	25	37.5	52
	4	17	75	85	85
	5	13	29	55	88
	6	11.7	23.5	55	68
	7	11.8	22	30	51
	8	16.6	38	56	67
	9	10	25	37.5	62.5
	10	5	22.5	55	67
Long term	11	11	21	60.5	84.2
	12	29	58	100	100
	13	11.8	37.7	64.8	70
	14	7.6	15.3	46.1	56.9
	15	12.5	25	37.5	74
	16	8.4	50	52.4	69.1
	17	16.6	50	52	69.1
	18	13	29	55	68
	19	12	23.5	41.1	82.3
	20	5	23	78	82.5
	21	33	66	77.3	100
	22	0	10	35.7	44.6
	23	16.6	38	56	67
	24	11.2	22.3	55.6	66.6
	25	0	22	60	56
	26	10	37.5	37.5	62.5
	27	4	32.2	40	80
	28	20	34	40	47
	29	12	38	70	78.8
	30	4	27	38	79

TABLE 3. *Duration of OP Treatment and Follow-Up Results*

OP treatment	Patient	IH thickness at beginning of treatment (mm)	IH type	Location of IH	Duration of treatment (months)	Relapse	Relapse onset after stopping treatment (months)	Follow-up after stopping treatment (months)
Short term	1	12	Deep	Periocular	4	Yes	3	27
	2	7.5	Combined	Genital	8	Yes	0.5	26
	3	10	Deep	Forehead	4	No	N/A	25
	4	19	Combined	Side	4	Yes	2	25
	5	31	Combined	Scalp	4	Yes	1	25
	6	17	Deep	Periocular	4	Yes	2	21
	7	14	Combined	Genital	4	Yes	4	21
	8	18	Combined	Periocular	5	Yes	2	22
	9	8	Deep	Nasal	5	Yes	3	22
	10	10	Deep	Lower lip	3	Yes	2	21
Long term	11	7.8	Combined	Lower lip	12	No	N/A	21
	12	15	Superficial and hepatic	Cutaneous and hepatic	12	No	N/A	21
	13	8.2	Combined	Upper lip and nasal	12	No	N/A	20
	14	10	Deep	Periocular	12	No	N/A	19
	15	17	Combined	Hip	12	No	N/A	19
	16	8.4	Combined	Cheek	12	Yes	2	18
	17	9	Combined	Lower lip	12	No	N/A	18
	18	15	Combined	Nasal	12	No	N/A	18
	19	4	Deep	Nasal	11	No	N/A	18
	20	4	Combined	Lower lip	12	No	N/A	16
	21	15	Deep	Cheek	12	No	N/A	16
	22	5.6	Deep	Nasal	12	No	N/A	15
	23	12	Combined	Cheek	11	No	N/A	13
	24	13	Deep	Lower lip	12	No	N/A	13
	25	9	Deep	Submaxillary	12	No	N/A	13
	26	6	Deep	Nasal	12	No	N/A	13
	27	10	Combined	Periocular	11	No	N/A	13
	28	10	Combined	Neck	12	No	N/A	13
	29	15	Deep	Submaxillary	12	No	N/A	12
	30	5	Combined, segmentary	Periocular, nasal, and upper lip	12	No	N/A	12

N/A, not applicable.

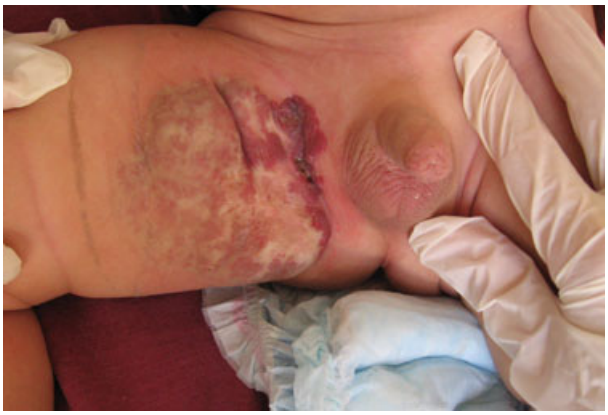

Figure 4. Patient 7. Ulceration recurrence during onset of relapse 4 months after stopping OP treatment.

factors cannot be excluded. For instance, in the group assigned to long-term therapy, OP was started at a younger age.

Longer OP therapy could be associated with more adverse effects, although both groups had a similar incidence of adverse effects, including mild bronchospasm, somnolence, and cold hands and feet, and there was a patient with an increase in transaminase levels in the short treatment group.

In both groups, to prevent hypoglycemia, we instructed parents and caregivers to feed the patients just before administering each dose of OP, and extreme caution was observed during systemic illness.

Finally, ultrasound together with monthly assessment of clinical responses allowed us to follow the patients' evolution in a close and objective manner and to regulate the OP dosage for mixed and deep IHs. The use of ultrasound to evaluate the response to treatment in this study was a useful tool in visceral, deep, and mixed IHs. In conclusion, long periods of OP treatment are related to fewer relapses. The small patient sample size in our study is an important limitation, as is it retrospective in nature.

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