Clinical evaluation of infantile hemangiomas treated with atenolol

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Abstract

Currently, propranolol, is the first line treatment for problematic infantile hemangioma (IH) management. However, serious side effects have been reported. For that reason, atenolol, a hydrophilic selective beta-1 blocker with the potential for fewer side effects, has been explored. A descriptive, observational case series study of 30 patients between the ages one to 5 months with superficial, deep, or mixed IH was conducted between January 2016 and December 2017. Oral atenolol was administered using a single once daily dose of 1mg/kg, which was adjusted for weight gain each month. The IH was assessed using the Hemangioma Activity Score (HAS) at initiation of treatment, four months, and 9 months of age and improvement percentage was calculated at four and nine months of age. A total of 25 patients completed three evaluations. The baseline, four-month, and 9-month HAS were 4.6, 2.39, and 0.65, respectively. Mean improvement percentage at four months of age was 46.76% and at 9 months of age was 85.65%. No side effects were reported. This study suggests atenolol as an effective treatment for IH in almost all cases, especially in patients who initiated treatment before three months of age. It was well tolerated in all our cases.

Keywords: infantile hemangioma, atenolol, beta-blocker, treatment

Introduction

Infantile hemangioma (IH) is the most common vascular tumor observed in infants with an incidence of 4% [1]. It is more frequent in female, preterm, and low birth weight infants. Other risk factors include multiple gestations, increased maternal age, placenta previa, and preeclampsia [2].

Infantile hemangioma is characterized by an early proliferative growth phase followed by a slower involuting phase. Infantile hemangioma is usually recognized within two or three weeks of age, reaching 80% of its final size at three months of age. The majority of IHs (both localized and segmental) complete their growth by 5 months of age. Based on this, the beginning of systemic treatment, if necessary, is ideally initiated before three months of age [3,4].

Propranolol, a non-selective lipophilic betablocker, has become the first line treatment for the management of complicated IHs since the first reports of its use in 2008 and approval by the FDA in 2014. Propranolol is associated with fewer adverse effects compared to oral corticosteroids, but also has potential side effects [5].

Among the side effects of propranolol bradycardia, hypoglycemia, and bronchial reactivity are the most serious [6]. However, purportedly because of its lipophilic nature, propranolol can cross the blood brain barrier and may increase the potential for central nervous system (CNS) adverse effects. There are many studies that show evidence of decreased short and long-term memory, decreased psychomotor function, and alteration in sleep quality and mood in healthy adults [7]. However, a retrospective study of 27 patients with IH treated with propranolol for more than 6 months during

infancy found no increased risk for psychologic problems at age of 7 years [8]. A recent meta-analysis did not observe statistically significant associations between oral propranolol and CNS or sleep-related effects in patients with IH [9].

Atenolol, a hydrophilic beta-1 blocker, reduces beta-2 activity at low doses and is less lipophilic. Therefore, it has a lower probability of causing CNS alterations [10]. Unfortunately, it has not yet been approved by the FDA because there are a limited number of studies that address the effectiveness of atenolol as a treatment of IHs, particularly in young infants.

We present our additional experience of 30 cases of IH that were treated with oral atenolol in the Pediatric Dermatology Service of the Instituto Nacional de Salud del Niño, Lima-Peru. Our objective was to evaluate the clinical response and the frequency of adverse effects.

Methods

The available data were collected from patients with superficial, deep, and mixed IHs treated with oral atenolol at a dose of 1mg/kg/day between January 2016 and December 2017, at the Pediatric Dermatology Service of Instituto Nacional de Salud del Niño, Lima, Peru. The research protocol was approved by a designated Institutional Review Board. The case series was studied in a descriptive, observational, and prospective manner.

Patients

Data from the patients of the Dermatology Service of the Instituto Nacional de Salud del Niño-Breña, Lima, Peru were included. The inclusion criteria were: 1) age of 1-5 months; 2) superficial, deep, and mixed IH that required systemic therapy; 3) minimum diameter of the surface IH greater than two cm; 4) IH of any size for those located in: periorbital, perioral, perinasal, and perineal regions; 5) ulcerated IH; and 6) complete and available clinical records. The exclusion criteria were: 1) patients who presented with contraindications for the administration of atenolol (bradycardia, acrocyanosis); 2) IHs that were previously treated with any type of therapy.

Treatment

Parents were informed about treatment with atenolol and gave consent for treatment. Personal and family history of any cardiac disease before starting the treatment was obtained. Atenolol was administered at a dose of 1mg/kg/day, twenty minutes after breast-feeding, once a day. Atenolol was compounded into a 5mg/2ml suspension for all patients at our center's compounding pharmacy. Insurance covered all atenolol prescriptions. The dose was adjusted according to the weight of the child, at each monthly visit. All those who had received at least one dose of atenolol and up to nine months of follow-up were included.

Monitoring and measurement of results

Patients were evaluated monthly until 9 months of age. Monitoring at each visit included the measurement of blood pressure and heart rate, as well as the reporting of adverse effects (lethargy, sleep disturbance, acrocyanosis, decreased appetite, diarrhea, vomiting, constipation, and difficulty breathing). Blood pressure was measured manually. Digital photographic records of the IHs were evaluated using the Hemangioma Activity Score (HAS) by two investigators independently [11]. The percentage improvement was calculated at four months and 9 months of age and compared to the initial evaluation. Additionally, patients who achieved 100% improvement were followed up to 12 months of age.

Results

Epidemiological characteristics of patients with infantile hemangioma

Thirty patients who met the inclusion criteria were included in the study. The epidemiological characteristics of patients with IH and the age of onset and the type of precursor lesion of IH are presented in **Table 1**. There were 27 females and three males with a female-male ratio of 9:1, and 80% were full-term newborns. With regard to maternal age, 77.7% of mothers were under 35 years of age. Only 11 patients (36.7%) had a significant history of fetal risk factors (preeclampsia, funicular dystocia,

Table 1. *The epidemiological characteristics of patients with infantile hemangioma.*

		n = 30	%
Sex	*Male*	3	10.0
	Female	27	90.0
Maternal age	*< 35 years*	7	27.7
	≥ 35 years	23	22.3
Gestational age at birth	*Preterm*	6	20.0
	Term	24	80.0
Perinatal history	*Preeclamspia*	3	10.0
	Funicular dystocia	7	22.3
	Placenta previa	1	3.4
	None	19	63.3
Family history of vascular anomalies	*Yes* *No*	9 21	30.0 70.0
Age at precursor lesion onset	*< 15 days* *≥15 days*	6 24	20.0 80.0

and placenta previa). Nine patients (30%) had a family history of vascular anomalies.

Clinical characteristics of infantile hemangioma

The most frequent location of IH was the head and neck (70%), followed by the trunk, extremities, and perineal area. All the IHs were localized. The superficial type (66.7%) was the most frequent, followed by the mixed (10%) and deep (23.3%) types. Infantile hemangiomas of the head and neck were located most frequently on the eyelids (33.3%).

Monitoring and evaluation of the resolution of hemangiomas

Twenty-five of the 30 subjects were evaluated at all three time points of the study. No adverse effects were reported and the heart rate and blood pressure were within normal values for age. Sixty percent of patients had treatment initiated by two months of age and 13.3% of patients started at one month of age. Infantile hemangiomas of that group were superficial, two of them on eyelids, one on the upper lip, and one on the left arm. The clinical evolution of the IHs were evaluated using the HAS are presented in **Table 2**, and **Figure 1**.

The mean HAS was calculated for patients who were evaluated at all three study time points. Baseline, four month, and 9 month HAS were 4.6, 2.39, and 0.65 respectively (**Figure 2**). The improvement at four months of age was 46.76% and 85.65% at 9 months of age. For patients who started treatment at one month of age, the improvement at 9 months of age of patients was 100%.

Discussion

There are an increasing number of reports in the medical literature of the use of atenolol as an alternative to propranolol for the treatment of problematic IH [12]. Many reports are small case series with a limited number of subjects that received treatment within the first few months of life. We present our experience of using atenolol in younger infants, with a single daily dose of 1mg/kg/day. In the present study, a favorable clinical response was observed in all patients with IH treated with atenolol at a dose of 1mg/kg/day, which was similar to other studies [13,14]. In a previous study, a 56.5% complete response rate was reported at 6 months of age in patients treated with atenolol [13]. Furthermore, a good response to atenolol has been described in patients who did not tolerate propranolol [14]. Similar to our results, assessment using the HAS found 100% improvement in 18 patients who were treated in the first 9 months of life, supporting the effectiveness of the beta blocker in the control of the phase of rapid growth of the HIs and induction of their involution [15].

The exact mechanism of action for beta blockers in the treatment of IH is unknown and several hypotheses have been proposed. Beta blockers may induce downregulation of proangiogenic growth factors (VEGF, bFGF) by inhibiting the renin-angiotensin pathway. Angiotensin II has been involved in the inhibition of progenitor cells towards the formation of adipocytes and also the inhibition of the apoptosis of mesenchymal and endothelial cells [16]. On the other hand, the presence of adrenergic receptors in IHs has been demonstrated. The β1 and β2 receptors allow the production of angiogenic factors and the β3 receptors are associated with lipolytic functions, so the use of non-selective beta blockers would allow the control of IHs in all their stages [17]. However, studies that compared both propranolol and atenolol did not find statistical differences [18,19] and reported

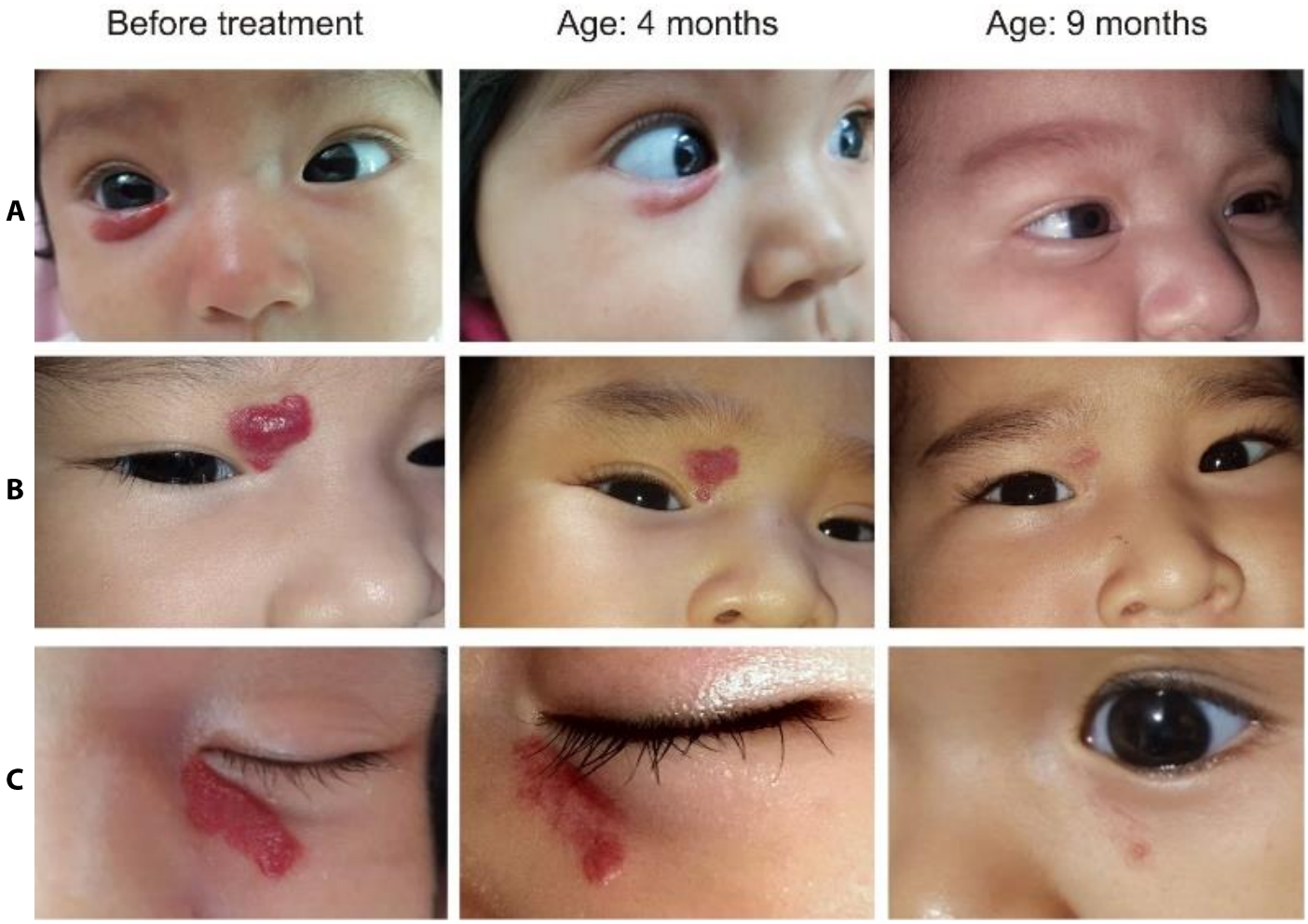

Figure 1. *Photographic records of patients with infantile hemangioma at eyelids with involution at 9 months of age. (A) Patient three started treatment at month of age. (B) Patient 15 started treatment at two months of age. (C) Patient 25 started treatment at two months of age.*

complete responses of 53.8% at 6 months with atenolol [20].

In our study, patients who initiated treatment before three months of age achieved improvement greater than 85% at the 9th month of age, but patients who initiated at one month of age reached 100%. This suggests that the treatment could be more effective when is initiated at an earlier age. This may avoid prolonged treatments and allow discontinuation of the medication before a year of life [21].

The treatment was withdrawn from the 18 patients who achieved a 100% improvement; after follow up at 12 months of age there was no evidence of rebound growth after discontinuation. Discontinuation of beta blocker therapy such as propranolol can be associated with a risk of rebound IH growth, mostly when it is withdrawn before 9 months of age [22]. A small sample size study reported two cases of rebound of 13 patients who were treated with atenolol for 6 months [20]. However, the factors associated with rebound in

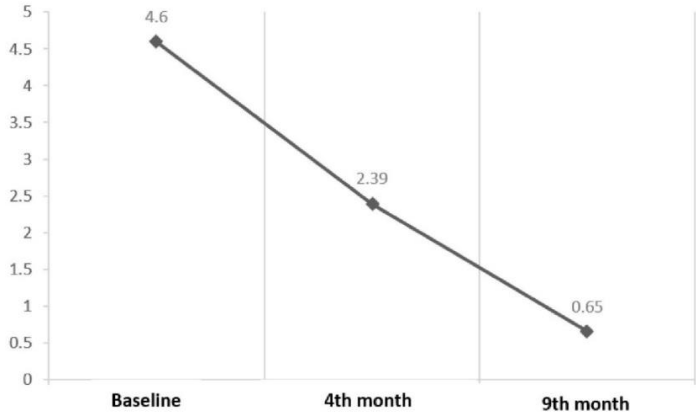

Figure 2. *Mean HAS of infantile hemangiomas treated with atenolol at the baseline, four months and 9 months of age.*

Table 2. *The clinical evolution of the infantile hemangiomas evaluated using the Hemangioma Activity Score.*

Patient	Age of treatment initiation	Baseline assessment	Response at 4th month old	Percentage of improvement (%)	Response at 9th month old	Percentage of improvement (%)
1	2 months	2	1.5	25	0	100
2	2 months	4	3	25	0	100
3	1 month	5	2	60	0	100
4	2 months	5	3	40	0	100
5	3 months	4.5	2	55.6	1.5	66.7
6	2 months	5	2	60	0	100
7	2 months	4	1.5	62.5	0	100
8	3 months	5	2	60	0	100
9	2 months	5	1.3	74	0	100
10	1 month	5	1.5	70	0	100
11[a]	4 months	5	-	-	4	20
12	2 months	5	4	20	3	40
13	2 months	5	2	60	0	100
14[a]	4 months	4	-	-	0	100
15	2 months	5	3	40	0	100
16	3 months	5	3	40	0	100
17[a]	5 months	5.5	-	-	1.3	76.4
18	2 months	5	1.3	74	0	100
19	3 months	5	4	20	1.3	74
20[a]	4 months	5	-	-	0	100
21[b]	1 month	5.5	3	45.5	-	-
22	2 months	4	3	25	1.7	57.5
23	2 months	4.3	3	30.2	0	100
24	2 months	3.7	3	19	3	19
25	2 months	5	1.7	66	0	100
26	2 months	5	4	20	3	40
27	1 month	3.5	2	42.8	0	100
28	2 months	5	2.5	50	1.3	74
29	2 months	5	2	60	1	80
30	2 months	5	1.5	70	0.5	90

[a]Patients who have an initial IH assessment after 4 months of age.
[b]Patients who only have an initial IH assessment at 4 months of age.

patients treated with atenolol are not currently known.

Less than 50% improvement was noted at the study endpoint in 5 patients. One patient achieved less than 20% improvement from baseline. Factors that might have contributed to limited improvement include late initiation of treatment at four months of age. Two patients who had their IHs located on the upper lip and lower lip respectively, reached a percentage of improvement of 40%. Parents of both patients report that they were noncompliant with the treatment and had treatment irregularities. Lack of compliance, as reported in a previous study, contributes to treatment failure [23]. Likewise, cases of poor response to propranolol have been reported in up to 10% and focal facial lesions failed to respond twice as frequently as other types of hemangioma [24], but this finding is not described with atenolol.

According to our results, poor responders to atenolol treatment often had midline, deep, and bulky lesions. However, owing to the small number of patients we can't conclude that this location is related to primary resistance to treatment. Additional studies with a larger cohort of patients would be needed in order to determine if this is an independent risk factor for poor response.

No side effects were noted in our cohort. Our results are consistent with other studies that found no

significant side effects [13,20]. Fewer side effects, such as diarrhea, acrocyanosis, agitation and sleep disturbance, have been reported with atenolol compared with propranolol [14,18]. Widely known propranolol-related serious adverse events, such as hypoglycemia, bronchospasm, bradycardia, and hypotension, have not been reported [12]. However, more studies with a greater number of patients, especially randomized controlled trials, are needed to compare effectiveness and safety of atenolol and propranol.

Conclusion

This prospective, observational case series demonstrated that atenolol was an effective treatment for problematic IH in almost all cases, especially in patients who initiated treatment before three months of age. The therapy was well tolerated in all cases.

Potential conflicts of interest

The authors declare no conflicts of interests.

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