

# Oral atenolol therapy for proliferating infantile hemangioma

## A prospective study

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### Abstract

Propranolol, a lipophilic nonselective  $\beta$ -blocker, has recently been reported to be the treatment of choice for select types of infantile hemangiomas (IHs). Atenolol is a hydrophilic, selective  $\beta_1$ -blocker and therefore may be not associated with side effects attributable to  $\beta_2$ -adrenergic receptor blockade and lipophilicity. However, the efficacy and safety of atenolol in the treatment of IH are poorly understood. The aim of this study was to evaluate the efficacy and safety of atenolol in the treatment of proliferating IHs.

A study of 76 infants between the ages of 5 to 20 weeks with superficial or mixed IH was conducted between August 2013 and March 2015. Oral atenolol was administered in a progressive schedule to 1 mg/kg per day in a single dose. Efficacy was assessed using the Hemangioma Activity Score (HAS) at weeks 0, 1, 4, 12, and 24. Safety was evaluated at weeks 0, 1, 4, 8, 12, 16, 20, and 24.

In total, 70 patients completed 24 weeks of treatment. IH growth abruptly stopped for 93.4% of patients within the fourth week of treatment with atenolol. In ulcerated IHs, complete healing of the ulcerations occurred in an average treatment time of 5.5 weeks. Atenolol treatment promoted dramatic decreases in HAS scores after week 1. An "excellent" treatment response (complete or nearly complete resolution of the IH) was observed in 56.5% of patients at week 24. No significant hypoglycemia, bronchospasm, bradycardia, or hypotension occurred. The most common adverse event was diarrhea, followed by agitation and sleep disturbance.

This study demonstrated that atenolol was effective and safe at a dose of 1 mg/kg per day for 24 weeks in the treatment of proliferating IHs.

**Abbreviations:**  $\beta$ -ARs =  $\beta$ -adrenergic receptors, CNS = central nervous system, HAS = Hemangioma Activity Score, IHs = infantile hemangiomas.

**Keywords:** atenolol, efficacy, infantile hemangioma, safety, tolerance

## 1. Introduction

Infantile hemangiomas (IHs) are the most common vascular tumors in children, with an estimated prevalence of 5% to 10%. Infantile hemangiomas are clinically heterogeneous, with their

appearance dictated by the location, depth, and stage of evolution. IHs may be located in any region of the body, including the internal organs, but are mostly located in the skin of the head, face, and neck region. Although many of these lesions resolve spontaneously without threat or complication, in some cases, IHs can grow dramatically and destroy tissue, impair function, or even threaten the patient's life.<sup>[1,2]</sup>

Previously, corticosteroids were the mainstay of treatment for complicated IHs. However, corticosteroids have undesired side effects, such as temporary growth retardation, an increased risk of infection, and behavioral changes.<sup>[3]</sup> Recently, propranolol, a nonselective  $\beta$ -blocker, became the preferred treatment for complicated or select types of IHs.<sup>[4]</sup> This medication can significantly reduce the need for surgery.<sup>[5,6]</sup> Currently, propranolol has become the first-line medical therapy for most clinicians that treat complicated IHs.

However, despite its efficacy, the use of propranolol in IHs is not without risk. Propranolol is a competitive antagonist of catecholamines at both the  $\beta_1$ - and  $\beta_2$ -adrenergic receptors ( $\beta_2$ -ARs).  $\beta_2$ -AR blockade may result in hypoglycemia. Long-term hypoglycemia in infancy has been associated with neurological morbidity. In addition, bronchial hyperreactivity is a direct effect of  $\beta_2$ -AR blockade.<sup>[7]</sup> Perhaps most importantly, the lipophilic nature of propranolol facilitates the crossing of the blood-brain barrier. Evidence derived from different groups has proven that propranolol can decrease long-term memory, psychomotor functions, sleep quality, and mood in adults.<sup>[8,9]</sup> Although studies in children are lacking, it has been postulated that there may be long-term effects of propranolol, which affect

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the developing central nervous system (CNS), specifically learning and memory, when given to infants.<sup>[10]</sup> Theoretically, a solution to minimize many of the potential side effects of propranolol may be the use of hydrophilic selective  $\beta_1$ -blockers, such as atenolol, which, at low dosages, have little  $\beta_2$  activity and are less likely to produce CNS-related side effects.<sup>[11]</sup> Unfortunately, there is a paucity of clinical data regarding the efficacy and safety of selective  $\beta$ -blockers (e.g., atenolol) in the treatment of IHs.

This report presents 76 cases with proliferating superficial or mixed IHs that were treated with oral atenolol. The objective of this study was to assess the efficacy, safety, and tolerance of oral atenolol in the treatment of IHs.

## 2. Methods

This study included patients diagnosed with superficial or mixed IHs and treated with oral atenolol from July 2013 to March 2015. Approval was obtained from the Ethics Committee of the West China Hospital of Sichuan University. All procedures followed the research protocols approved by Sichuan University and the West China Hospital of Sichuan University and conducted according to the Declaration of Helsinki. Written informed consent for the use of clinical records was provided by the patients' parents.

### 2.1. Patients

All patients were recruited at Department of Pediatric Surgery, West China Hospital of Sichuan University. The criteria for inclusion were as follows: (1) the patients were between the age of 5 weeks and 20 weeks; (2) a superficial or mixed proliferating IH that required systemic therapy; (3) the minimum diameter of the IHs should be 1.5 cm on the face, 3 cm outside the face or 1.5 cm if ulcerated; and (4) cConsent of both parents (or the person with parental authority). The exclusion criteria were: (1) patients that presented contraindications to the administration of atenolol; (2) IHs previously treated with corticosteroids, laser therapy, cryotherapy, or other treatments; and (3) patients unable to follow the assessment plan.

### 2.2. Treatment regimen

The parents were informed that atenolol was prescribed for the treatment of IHs and they gave consent for its use. Before starting atenolol, each child underwent echocardiography to exclude contraindications to atenolol treatment. Atenolol was initiated at a dosage of 0.5 mg/kg per day in a single dose for 1 week, and then increased to 1 mg/kg per day in a single dose from weeks 2 to 24. We requested that atenolol be administered in the morning and within 30 min after the patients were fed. The dosage of atenolol was adjusted for weight at each visit.

### 2.3. Monitoring of identified risks and outcome measures

Patients were evaluated at weeks 0, 1, 4, 8, 12, 16, 20, and 24. Baseline screening comprised blood pressure, heart rate, and blood glucose. Patients' heart rates were recorded prior to the initiation of treatment, and at 1, 2, 4, and 8 hours following the first dose of 0.5 mg/kg per day and the next week at 1 mg/kg per day. In addition to heart rate, the patients' blood pressure, blood glucose, growth, and development were monitored at each visit. During follow-up, the frequency of adverse events (e.g., lethargy,

sleep disturbance, cool or mottled extremities, poor appetite, diarrhea, etc.) were reported by parents and collected by investigators.

Photographs of IHs were taken at weeks 0, 1, 4, 12, and 24 and were independently assessed by 2 investigators (SYC and QW) using the Hemangioma Activity Score (HAS).<sup>[12]</sup> The outcomes were classified as excellent (complete or nearly complete resolution of the IH), good (partial resolution), stable (no further growth), or deterioration at week 24 versus baseline according to the evaluation. In the case of multiple IHs, only the clinically most important IH (typically the largest or ulceration IH) was documented.

## 3. Results

### 3.1. Patient demographics and IH characteristics

A total of 76 children met the criteria for inclusion and were enrolled in the study. The main baseline characteristics of patients and IHs are presented in Table 1. There were 17 males and 59 females, with a male-to-female ratio of 1:3.47. The mean age at the start of atenolol treatment was 10.0 weeks (SD=3.7, range 5–20 weeks). The head–face–neck area was the dominant location, representing 50% of all IHs, followed by the extremities, trunk, and perineal area. Among IHs in the cohort, 72.4% were of the localized morphologic subtype and 88.2% were mixed hemangiomas (Table 1).

Hemangioma ulceration was observed in 9 patients. The mean age of the start of atenolol was 12.2 weeks. In these patients, ulceration-associated pain resulted in problems with feeding, sleeping, defecation, and/or secondary infection.

In total, 70 patents completed 24 weeks of treatment. A total of 6 patients withdrew from the study: 2 patients discontinued treatment after week 8, 3 patients after week 12, and 1 patient after week 16. Lack of efficacy was the most frequent reason for

**Table 1**  
Baseline characteristics of patients and infantile hemangiomas.

Characteristic	n (%)
Patients	
Gender	
Male	17 (22.4)
Female	59 (77.6)
Gestational age	
Term born	68 (89.5)
Born prematurely	8 (10.5)
Age at treatment	
5–10 w	45 (59.2)
11–15 w	22 (28.9)
16–20 w	9 (11.8)
Infantile hemangiomas	
Location	
Head, face, and neck	38 (50.0)
Extremity	19 (25.0)
Trunk	13 (17.1)
Perineal area	6 (7.9)
Morphologic subtype	
Localized	55 (72.4)
Segmental	11 (14.5)
Indeterminate	10 (13.1)
Description	
Superficial	9 (11.8)
Mixed	67 (88.2)

w = week.

discontinuation (4 patients). Other reasons included the parents' choice and treatment intolerance for 1 patient each.

### 3.2. Efficacy

IH growth abruptly stopped for 93.4% of patients within 4 weeks of atenolol treatment. This effect was remarkable in infants who initiated therapy during the early proliferative phase (Fig. 1). Rapid therapeutic effects, including changes in the color of the IH, reduction in the size of the mass, and softening of the texture, were observed in early treatment. IHs continued to regress progressively after the rapid initial response, as shown in Fig. 2.

Of the 9 patients with ulcerated IHs, 7 were additionally treated with wound dressings and/or oral antibiotics during atenolol treatment. After introducing oral atenolol, complete healing of the ulcerations occurred within 8 weeks of treatment in all patients (Fig. 3). Complete healing of the ulcerations was obtained in an average treatment time of 5.5 weeks.

Referring to the treatment response at week 24, an "excellent" response was observed in 43 patients (56.5%), "good" in 20 (26.3%), "stable" in 6 (7.9%), and "deterioration" in 2 (2.6%). The HAS results scored by the investigators are shown in Fig. 4. Atenolol treatment promoted dramatic decreases in the HAS scores after week 1.

### 3.3. Safety and tolerance

During the 8 hours after the initial atenolol treatment and after the first dose adjustment, the mean heart rate decreased. We found that the heart rate decreases occurred within 1 hours and were most apparent at 2 hours after atenolol administration. Then, the heart rate gradually increased. The average decrease in the heart rate was ~11 beats per minute 2 hours after every dose (Fig. 5).

All known adverse effects of  $\beta$ -blockers were recorded at each visit. Well-known severe adverse events, including hypoglycemia, bronchospasm, bradycardia, and hypotension, were not documented. The most common event was diarrhea. In 89.5% (17/19)

of cases, the symptoms of diarrhea were classified as mild or moderate in severity. Other common events reported by parents were agitation, sleep disturbance, and vomiting. These side effects subsided without requiring any further medication. Less common events included constipation and cool or mottled extremities. Several patients developed respiratory events: 6 patients developed bronchiolitis and 3 patients developed viral upper respiratory tract infection. One young child (5-week-old girl) experienced transient lethargy during the first dose-adjustment phase. Her blood glucose, carefully measured by paramedics, was normal (Table 2).

Atenolol was generally well tolerated in children. Four patients required a rest period of 3 to 10 days prior to resuming treatment due to diarrhea (2/4), bronchiolitis (1/4), and hemorrhagic enteritis (1/4). In 1 patient (a 9-week-old girl with perineal IH) who developed hemorrhagic enteritis after 16 weeks of treatment, atenolol was temporarily suspended until the child recovered. However, the girl had bloody stool again after resuming atenolol treatment. Therefore, oral atenolol was permanently discontinued in this patient.

## 4. Discussion

Previously, a small number of studies showed that oral atenolol had a positive role in reducing the progression of problematic IHs, but these findings were based on relatively small sample sizes.<sup>[13-15]</sup> Therefore, to confirm the effects of atenolol in the treatment of IHs, more extensive clinical studies are required. In the present study, we successfully provided further clinical evidence of the efficacy, safety, and tolerability of oral atenolol in young patients (mean age 10.0 weeks) with proliferating IH. Regardless of subtype or depth, IHs reached 80% of their final size during the first 3 months, with most IH growth completed by 5 months of age.<sup>[16]</sup> Thus, the majority of our patients began treatment before the growth was over.

Our study demonstrated that patients who received oral atenolol at a dose of 1.0 mg/kg per day for 24 weeks exhibited a 56.5% rate of successful treatment (complete or nearly complete



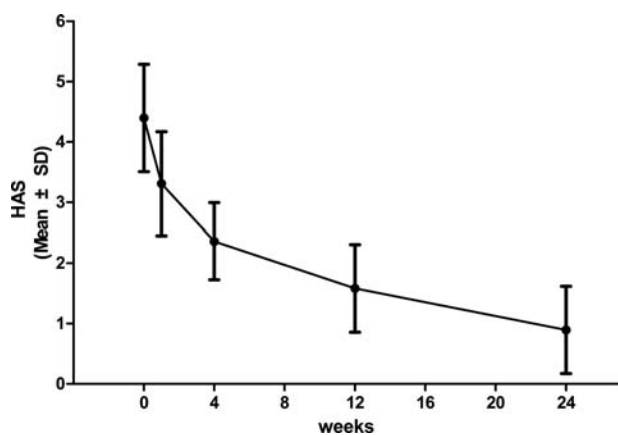
**Figure 1.** A girl with left subaural infantile hemangioma (IH) treated with atenolol. (A) At 3 weeks of age, 2 weeks before treatment with atenolol. Clinical photographs of IH at baseline (B), 1 (C), 4 (D), 12 (E), and 24 (F) weeks after the start of treatment. IH=infantile hemangioma.



**Figure 2.** Clinical photographs of patients treated with atenolol showing changes in the color and size of the lesion at weeks 0, 1, 4, 12, and 24: (A) 5-week-old girl with right temporal IH; (B) 6-week-old girl with IH on the left forearm; (C) 8-week-old girl with mixed IH on the left chest; (D) 10-week-old boy with IH on the left shoulder; (e) 20-week-old girl with IH on the right shoulder. IH=infantile hemangioma.

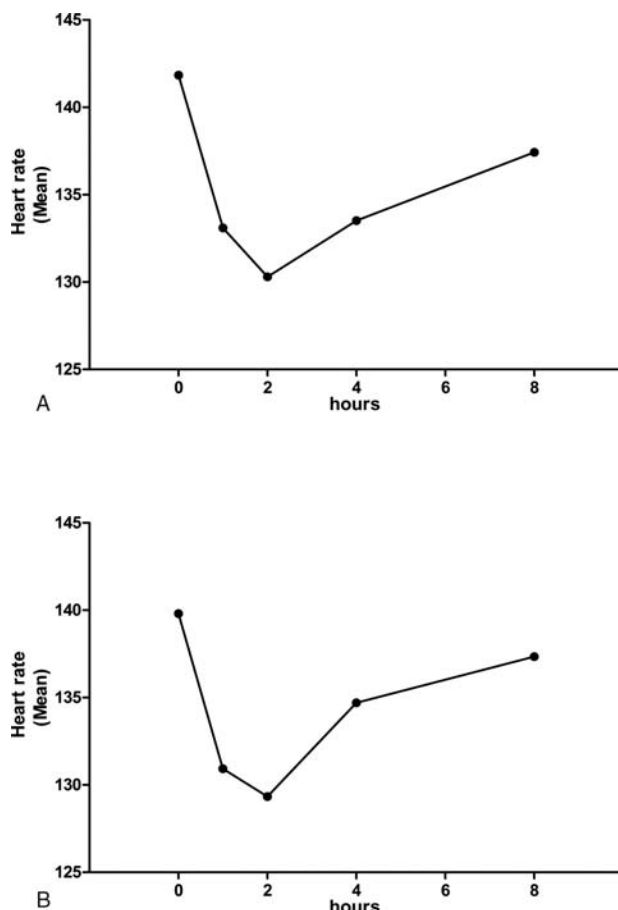


**Figure 3.** A 9-week-old boy with ulcerated IH on the scrotum. Clinical photographs of IH at baseline (A), 1 (B), 4 (C), 12 (D), and 24 (E) weeks after the start of treatment. IH=infantile hemangioma.



**Figure 4.** Hemangioma Activity Score (HAS) of the efficacy of atenolol. The efficacy of atenolol was scored at week 0, 1, 4, 12, and 24. HAS, Hemangioma Activity Score.

resolution of the target IH). Previously, a small randomized controlled trial showed no significant difference in effectiveness between atenolol and propranolol.<sup>[15]</sup> Similar results were also shown in a study by Graaf and colleagues, although it is noteworthy that the dosage of atenolol was increased to a



**Figure 5.** Changes in the heart rate during atenolol treatment: (A) the mean heart rate before and after the first dose of atenolol at week 0; (B) the mean heart rate before and after the first dose adjustment at week 1.

maximum of 3 mg/kg per day.<sup>[13]</sup> Like propranolol, atenolol can stabilize IHs in their growth phase. According to the growth characteristics of IHs, there is a period of rapid proliferation between 5.5 and 7.5 weeks of age.<sup>[17]</sup> Because  $\beta$ -blocker treatment is not only effective in arresting growth but also causes significant involution, treatment may be more effective when implemented before most of the growth has already occurred. In our patients, the natural course of IHs was considerably shortened, especially for those lesions in the early proliferative phase. These data further support the concept that earlier evaluation and intervention improve outcomes. Therefore, for IHs that require treatment, the ideal time to begin treatment may be before or as soon as evidence of permanent anatomic distortion or medical sequelae develops.<sup>[18]</sup> We can anticipate that the age at which treatment is initiated is likely to be lower as we become more aware of the use of  $\beta$ -blockers as a safe and effective treatment for IHs and become comfortable with its use in very young infants.

By monitoring heart rate every 4 weeks and more frequently after initial treatment and after the first dose adjustment, our data demonstrated that the reduction in the heart rate was not sustained in infants treated with atenolol. Although the mean heart rate decreased, all recorded heart rates and blood pressures were within the normal range. Remarkably, results from recent case control studies, including a randomized controlled trial of oral propranolol in 460 patients, were also exciting, with all studies showing that propranolol had no significant sustained effects on heart rates in infants with IH.<sup>[18]</sup> These observations, together with the work presented here, suggest that the cardiovascular risks of the use of  $\beta$ -blockers in IH patients may be lower than we initially feared.

Clinical studies that addressed the adverse effects of atenolol on children with IH have generated conflicting results. In a study by Abarzua-Araya et al.<sup>[15]</sup> the authors showed no significant adverse event in atenolol treatment during the 6-month follow-up. Additionally, the authors demonstrated no adverse events after propranolol treatment. In the present study, any adverse events were recorded by parents between study visits and were documented by investigators at each visit. Although serious adverse effects were rare, adverse effects, such as gastrointestinal events, respiratory events (e.g., bronchiolitis) and CNS-related side events (e.g., agitation and sleep disturbances), were still frequently seen. The most common event, diarrhea, was the main reason for temporarily discontinuing atenolol. However, the efficacy of treatment in patients who had a history of temporarily discontinuing treatment could not be statistically analyzed because of the small sample size. In addition, there is no explanation for why there is a high incidence of diarrhea in children treated with atenolol. The appearance of hemorrhagic enteritis in 1 patient was unexpected. Whether hemorrhagic enteritis was a manifestation of adverse gastrointestinal effects or an incidental event is unclear based on our cases. Further studies are needed to establish the significance of this phenomenon. Sleep disturbance is generally considered to be a side effect attributable to the lipophilic character of propranolol. In the current series, ~11.8% of patients experienced sleep disturbance. However, it is noteworthy that in the placebo-controlled study with propranolol, sleep disturbance was as high as 13% in the placebo group (as opposed to 14–29% with 1–3 mg/kg propranolol).<sup>[19]</sup> Therefore, further studies including both placebo (or propranolol) and atenolol treatment are needed to extend our findings.

In the present study, the inclusion criteria were uniformly standardized. Only patients between of 5 and 20 weeks of ages

**Table 2**  
**Adverse events that occurred during the 24 weeks of atenolol treatment.**

Adverse events	Week 1 n=76	Week 4 n=76	Week 8 n=76	Week 12 n=74	Week 16 n=71	Week 20 n=70	Week 24 n=70	Total* n=76
Diarrhea	5	6	3	3	1	0	1	19 (25.0)
Agitation	5	2	3	1	0	1	0	11 (14.5)
Sleep disturbance	3	3	1	3	0	1	0	9 (11.8)
Vomiting	2	2	1	2	0	2	0	9 (11.8)
Constipation	1	0	0	2	2	1	1	7 (9.2)
Cool extremities	3	2	1	0	1	0	0	6 (7.9)
Bronchiolitis	0	2	1	0	3	0	0	6 (7.9)
Poor appetite	0	0	1	2	0	1	0	4 (5.3)
Viral upper respiratory tract infection	0	0	1	1	0	1	0	3 (3.8)
Lethargy	0	1	0	0	0	0	0	1 (1.3)
Hemorrhagic enteritis	0	0	0	0	1	0	0	1 (1.3)

\* Values are presented as numbers (percentage).

and patients with superficial or mixed IHs were included. All treatments were initiated at proliferating phase of the disease. The strict inclusion criteria provided the way to overcome the selection and ascertainment bias. In addition, the dosage and schedules for atenolol were standardized. Strengths of the present study also included the inclusion of a validated/standard assessment (HAS) of the evolution of IHs and regular follow-up. Assessment of our outcomes involved standardized photographic procedures and independent reading. The data from these standardized procedures provided a wealth of information.

In the 8 years since June 2008, when Leaute-Labreze et al<sup>[4]</sup> first reported their serendipitous discovery that oral propranolol is effective in the management of severe IHs, many articles on  $\beta$ -blocker therapy for IHs have been published. Although substantial progress has been made in understanding the roles of  $\beta$ -blockers in the treatment of IH, several issues still need to be addressed. What are the optimal doses and schedules of oral  $\beta$ -blockers in young infants with IHs, as sensitivity to  $\beta$ -blockers has exhibited ethnic or racial differences?<sup>[20,21]</sup> Do  $\beta$ -blockers affect the developing CNS of infants? Do nonselective  $\beta$ -blockers (e.g., propranolol) have significantly better efficacy, but fewer adverse effects than selective  $\beta$ -blockers (e.g., atenolol), or vice versa? How do  $\beta$ -blockers trigger the involution of IH? These issues should be the topics of further studies.

**5. Conclusions**

In conclusion, this study in infants aged 5 to 20 weeks revealed that 1 mg/kg per day in a single dose of atenolol for 24 weeks is an effective and safe therapy for the treatment of proliferating IH. Our study demonstrated the benefits of atenolol in patients with proliferating IH. These findings not only provide evidence to show that atenolol may be an alternative in the treatment of IHs but also valuable data for further clinical investigations. Further efforts are needed to evaluate and verify these findings to achieve a greater understanding of the efficacy and safety of atenolol in the treatment of IHs.

**5.1. Consent**

Written informed consent regarding the publication of this study and the accompanying images was provided by the patients' parents. Copies of the signed informed consent forms are available for review by the Series Editor of Medicine.

**5.2. Ethical approval**

This study was approved by the Ethics Committee of the West China Hospital of Sichuan University. Written informed consents were obtained regarding the use of the images in accordance with the Declaration of Helsinki.

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