ORIGINAL ARTICLE

Atenolol versus propranolol for the treatment of infantile hemangiomas: A randomized controlled study

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Background: Infantile hemangiomas have a dramatic response to propranolol, a nonselective beta-blocker. However, this treatment is not risk-free and many patients are excluded because of respiratory comorbidities. Atenolol is a cardioselective beta-blocker that may have fewer adverse events.

Objective: We sought to evaluate the effectiveness of atenolol against propranolol in a noninferiority trial.

Methods: In all, 23 patients met the inclusion criteria and were randomized to receive either atenolol or propranolol. Thirteen patients were treated with atenolol and 10 with propranolol. Follow-up was made at baseline, 2 weeks, 4 weeks, and then monthly for 6 months.

Results: Patients treated with atenolol had a complete response of 53.8% and 60% with propranolol, respectively. These results were nonsignificant (P = .68). Relevant adverse events were not reported.

Limitations: The reduced number of patients could have influenced our results.

Conclusion: Atenolol appears to be as effective as propranolol. We did not find significant differences between these results or any adverse events. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.01.905.)

Key words: atenolol; beta-blockers; hemangiomas; propranolol; randomized; treatment; trial.

Infantile hemangiomas (IH) are the most common vascular tumor of infancy.[1-6] In the vast majority of patients, treatment is not necessary and only strict follow-up is recommended[6]; however, in about 10% of IH, intervention is required.[7,8]

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 or a combination of these treatments.[3,6-13]

Propranolol, a nonselective β1 and β2 antagonist, was shown to be an effective therapy for IH.[8] Since the serendipitous findings of Léauté-Labrèze et al[14] in 2008, many case reports and case series have shown the efficacy of propranolol in IH.[6,15] Still, its use is not risk-free and many adverse events have been documented, including: hypoglycemia, bronchial obstruction, hypotension, seizures, sleep disturbances, and gastrointestinal symptoms, among others.[6,16]

Abbreviations used:

CR:	complete response
ECG:	electrocardiogram
HR:	heart rate
IH:	infantile hemangioma

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On the other hand, atenolol, a hydrophilic cardioselective beta-blocker that acts principally on $\beta 1$ receptors, does not cross the blood-brain barrier and has less $\beta 2$ effects.[17,18] However, it has limited use in pediatric patients.[19] To date, some authors have demonstrated that atenolol is safe and effective in children with cardiologic pathologies. Ko et al[17] used atenolol in 22 patients younger than 5 years for the treatment of supraventricular tachycardia without adverse events. Local experience confirms that atenolol is safe and effective in infants and is frequently used for the treatment of supraventricular tachycardia without significant adverse events.[17,20-22]

Raphaël et al[23] reported 2 patients with IH presenting adverse events with propranolol. They switched to atenolol with excellent response of the hemangiomas and with no secondary effects.

We propose the hypothesis that atenolol is at least as effective as propranolol in the treatment of IH.

CAPSULE SUMMARY

- Propranolol has been used for the treatment of infantile hemangiomas.
- Atenolol, a cardioselective beta-blocker, may be at least as effective as propranolol for the treatment of infantile hemangiomas.
- Patients with respiratory diseases may be treated with atenolol with the theoretical lower risk of bronchial obstruction and other adverse events.

METHODS

A randomized controlled noninferiority trial evaluating the efficacy of atenolol against propranolol for the treatment of IH was done between June 2012 and January 2013 at our department. The protocol was approved by our institutional review board.

Our primary objective was that atenolol was not inferior to propranolol for the treatment of IH. The secondary objective was to evaluate the adverse events of atenolol and propranolol.

Patients

Inclusion criteria were infants and children from 1 to 15 months old with IH needing treatment defined as: functional impairment, aesthetic disfigurement, and if they were ulcerated or located on folds.

A complete history, physical examination, and a baseline electrocardiogram (ECG) were performed. A pediatric cardiologist evaluated the patient before enrollment. Laboratory assessments were not required, unless symptom-driven.

Exclusion criteria were history of allergy or hypersensitivity to beta-blockers, second- or third-degree atrioventricular block, heart failure, severe bradycardia, asthma or bronchial obstruction, and previous use of systemic corticosteroids or other beta-blocker.

Treatment protocol

Patients who met inclusion criteria were randomized by simple randomization to receive atenolol 1 mg/kg/d for 6 months in a single daily dose, or propranolol in a dose of 2 mg/kg/d in 3 daily doses for 6 months. Allocation concealment was respected.

Blinding

The drugs were similar in aspect (capsules) and the patients and main investigators were blind.

Follow-up

Patients were evaluated at baseline, 2 weeks, 4 weeks, and then monthly until 6 months of treatment were completed. This protocol was done in an outpatient environment.

Primary objective was evaluated in every visit clinically and with digital camera photographs.

The response was classified as follows:

Complete response (CR) was defined as complete resolution of IH. Telangiectasia and redundant tissue were still considered CR.

Partial response was defined as any size reduction, or change in color or consistency that did not meet the CR criteria.

No response was defined as no change between photographs and/or growth while in treatment.

Adverse reactions reported by the parents or noted by the investigators were recorded.

In every visit we measured heart rate (HR), blood pressure, and heart failure symptoms (eg, dyspnea during feeding, sweating, and difficulty thriving) and symptoms of bronchial obstruction.

Cardiologic follow-up

At 48 to 72 hours after treatment start, patients were clinically evaluated by a pediatric cardiologist. Seven to 10 days after treatment initiation, they were evaluated with a 24-hour ECG Holter. If HR or blood pressure was altered or any symptom was present, treatment was withdrawn and all patients were sent to a new evaluation with a pediatric cardiologist.

Statistical analysis

Analysis was done by intention to treat.

Descriptive statistics were calculated using numbers with percentages or means and SD. To evaluate response we used Fisher exact test.