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.

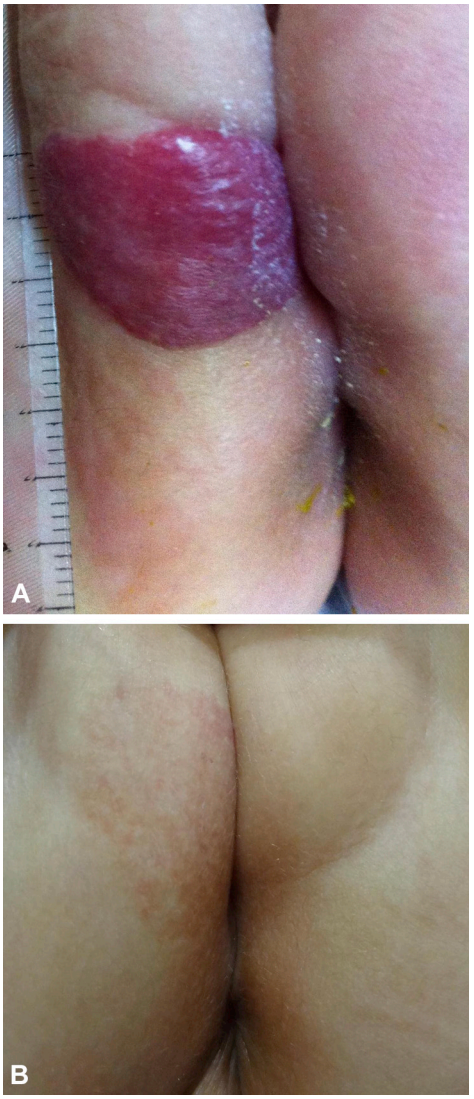

Fig 1. Hemangioma on vulva untreated (**A**) and with complete response to atenolol at 6 months (**B**).

For the noninferiority hypothesis we used Bayesian statistics. For HR analysis we used Freeman-Halton test. Data were analyzed using STATA 10.0 (StataCorp 2007, Stata Statistical Software, College Station, TX). Statistically significant results were considered with a *P* value less than or equal to .05 (confidence level of 95%).

RESULTS

Twenty-three patients were included in the study and started beta-blockers.

Of them, 15 of 23 (65.2%) were female and 34.7% were male. Mean age at the start of the study was 5.2 ± 3.5 months (range 2-14 months). There were not statistical differences between groups.

Thirteen patients were randomized to atenolol and 10 patients to propranolol. No patient was lost from follow-up. There were 35 IH with a number of hemangiomas per neonate of 1.5. Four patients (17.3%) had more than 1 IH and 1 patient had 9 hemangiomas (multiple hemangiomas defined as >5 IH). This patient did not have visceral or intracranial hemangiomas (studied with abdominal and cerebral ultrasonography). There were no segmentary hemangiomas. By type, 16 hemangiomas were superficial, 16 were mixed, and 3 were deep IH.

By location, 20 of 35 (57.1%) were on head and neck. Five IH (14.2%) were on extremities. One was in the genitalia and 1 in the lumbar region. Patients with periocular IH were evaluated by the ophthalmologist; none of them had visual alterations requiring additional treatments.

There was only 1 patient with an ulcerated hemangioma in the parotid area. He received additional treatment with oral cefadroxil and topical 2% mupirocin. He had an excellent response at 1 month follow-up. He was not evaluated by an otolaryngologist.

No patient required hospitalization during the study for initiation of treatment and all patients received beta-blockers in an outpatient environment.

Efficacy

We found a CR of 7 of 13 (53.8%) patients for atenolol (Fig 1) and 6 of 10 patients (60%) for propranolol. Partial response was 6 of 13 (46.1%) for atenolol and 4 of 10 (40%) for propranolol. These differences were not statistically significant ($P = .68$).

When evaluating the response rate by type of hemangiomas, we found a CR of 5 of 9 (55.5%) for superficial hemangiomas and a CR of 3 of 13 (23%) and 3 of 3 (100%) for patients with mixed and deep IH, respectively (we did not perform statistical analysis because of small sample size).

Adverse events

There was no significant adverse event in any group of treatment during the 6-month follow-up. Neither ECG nor 24-hour ECG Holter result was altered in any patient. Mean HR was 127.3 bpm (range 61-203 bpm), without differences between both drugs ($P = .82$). All patients were asymptomatic. Mean blood pressure was 70.3 mm Hg (range 64-81 mm Hg) within normal range in all patients and without differences between groups ($P = .2$).

No patients had gastrointestinal symptoms, intercurrent diseases, or signs/symptoms suggestive of hypoglycemia requiring prompt study, laboratory workup, or withdrawal of the drugs.

Rebound

Regrowth of the IH when the medication was withdrawn was noted in 6 patients (26%): 4 on

propranolol and 2 on atenolol. These differences were nonsignificant. In all of them the drugs were reintroduced and the previous response rate was found.

DISCUSSION

To date, many studies and case series have established the use of propranolol in the treatment of IH.[1,2,6,9,10,13-15,24-33] Nevertheless, there is only 1 publication evaluating the use of atenolol in the treatment of IH.[23] To our knowledge, this is the first randomized controlled trial evaluating the efficacy and safety of atenolol compared with propranolol in the treatment of IH.

We found a CR of 53.8% for atenolol and 60% for propranolol without statistically significant differences between them. This rate of CR is very similar to the response rate of other studies. These preliminary data demonstrate that there may be no differences in response or in rebound rates between atenolol and propranolol. It is noteworthy that no IH grew or showed lack of response while in treatment independently of the drug used, a finding that was already reported.[15] A recent study found less than 1% of "absence of response" with propranolol in 109 patients.[31]

We analyzed adverse events with a strict follow-up and with a pediatric cardiologist evaluation and we did not find any severe adverse event that required withdrawal or modification of treatment or biochemistry analysis/examinations. Moreover, we did not record any patient presenting signs or symptoms of hypoglycemia, hypoperfusion, or heart failure.

A recently published systematic review was used to define the cut-off values for the percentiles of HR in our patients.[34]

These data should be interpreted with caution, as our results are certainly limited by the reduced number of patients; however, they are an initial approach for considering atenolol a new promising alternative for the treatment of IH.

Other authors have reported many adverse events with propranolol use.[16,32]

Atenolol was only evaluated in 1 publication with 2 patients and the authors did not report any adverse event.[23] Theoretically, atenolol has a selective beta-blockade sparing $\beta 2$ adrenergic receptors reducing the feared and reported bronchial adverse events of propranolol. This advantage could be used in patients with IH and obstructive bronchial pathology who are many times excluded from propranolol prescription. Furthermore, as it does not cross the blood-brain barrier it avoids the sleep disturbances associated with propranolol. Finally, by evading the $\beta 2$ blockade we would avoid the risk of hypoglycemia diminishing the interference with the gluconeogenesis, glycogenolysis, and lipolysis processes.[16]

Also, our study provides more evidence for the outpatient initiation and maintenance of beta-blockers, without the need of transient hospitalizations even in infants younger than 8 weeks of corrected age, as recommended in recent guidelines.[35] This has been previously assessed by our group and others.[15,36] In addition, atenolol has the advantage of once-daily regimen in contrast to propranolol.[35] This certainly may improve adherence of patients.[15,37,38]

To our knowledge, we have presented the first study evaluating atenolol against propranolol for treatment of IH. There may be no differences in response rates between both beta-blockers but atenolol has the advantage of a daily-dose administration and a possible reduced number of $\beta 2$ adverse events.

More studies are needed to confirm these preliminary results; however, we propose that atenolol could be added to the therapeutic arsenal for the treatment of IH.

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