Hemangiomas of the Nasal Tip Treated with Propranolol

Dan Ben-Amitai\textsuperscript{a, e} Shlomit Halachmi\textsuperscript{d} Alex Zvulunov\textsuperscript{a, f} Eyal Raveh\textsuperscript{b, e} Eyal Kalish\textsuperscript{c} Moshe Lapidoth\textsuperscript{d, e}

Units of \textsuperscript{a}Pediatric Dermatology, \textsuperscript{b}Pediatric Otorhinolaryngology and \textsuperscript{d}Pediatric Plastic Surgery, Schneider Children’s Medical Center, and \textsuperscript{e}Laser Unit, Department of Dermatology, Rabin Medical Center, Petah Tikva, \textsuperscript{c}Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, and \textsuperscript{f}Faculty of Health Sciences, Medical School for International Health, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Key Words
Nasal tip hemangiomas · Children · Propranolol

Abstract
Background: Infantile hemangioma is the most common tumor of infancy. There are recent reports of the efficacy of propranolol in the treatment of these hemangiomas. Nasal tip hemangiomas pose a particularly sensitive concern aesthetically and functionally. The treatment of nasal tip hemangiomas is controversial. We assessed the effect of propranolol therapy in hemangiomas of the nasal tip. Objectives: To evaluate the response of nasal tip hemangiomas to systemic propranolol. Methods: During 2008–2010 ten infant with nasal tip hemangiomas presented to our tertiary care center. All underwent comprehensive evaluation by a multidisciplinary team and were then treated with oral propranolol at 2 mg/kg/day, with continuous clinical follow-up until age 14–16 months, or in older infants until the proliferative phase resolved. Results: Eight patients demonstrated good clinical improvement. Two patients had partial improvement. One patient discontinued treatment due to wheezing. Three patients had mild sleep disturbance which did not warrant discontinuation of treatment. No rebound was noticed after cessation of treatment. Limitations: Children presented by referral at variable ages. It is possible that routine initiation of propranolol in neonates at the first sign of nasal hemangioma may reduce the required treatment duration or dose. Conclusions: Early treatment of hemangiomas of the nasal tip with propranolol prevents lesion proliferation, reduces lesion volume, and prevents nasal and facial deformation. Propranolol appears to be a safe and effective treatment. Its efficacy and safety profiles, relative to other accepted therapies, suggest that it should be considered as the first-line treatment when intervention is required.

Introduction

Infantile hemangioma is a benign tumor that occurs in 4–10% of infants, with a slight female predominance [1]. Most hemangiomas involve the head and neck; of these, 15% involve the nose and 5% involve the nasal tip [2, 3]. Nasal tip hemangiomas are generally subcutaneous, and their soft-tissue infiltration can distort the underlying cartilage. Unlike the usual spontaneous involution observed in infantile hemangiomas, nasal tip hemangiomas tend to regress slowly if at all. They notoriously give rise to permanent scarring and disfigurement, resulting in a
Cyrano’ or ‘Pinocchio’ appearance, with profound psychological impact [4, 5]. Management of nasal tip hemangiomas is challenging and controversial. Current treatment modalities include corticosteroids, laser, and surgical procedures [6–10]. Each of these approaches has limitations in therapeutic benefit and inherent risks. Since the dramatic response of hemangiomas to systemic propranolol was first reported as a serendipitous observation in 2008, propranolol therapy has rapidly gained acceptance for the treatment of classic infantile hemangiomas [11, 12]. Given that most infantile hemangiomas involute spontaneously, whereas nasal tip hemangiomas are generally more persistent and more resistant to therapy, we assessed whether propranolol is an effective treatment for this difficult-to-treat subtype.

Methods

The study was conducted at the Schneider Children’s Medical Center of Israel, a university-affiliated tertiary care hospital, and was approved by the Medical Center review board. The study was performed with a retrospective, comparative, interventional study design. The study group was comprised of 10 children who were diagnosed with isolated nasal tip hemangiomas from 2008 to 2010, and who were treated with propranolol. The diagnosis of hemangioma was based on clinical examination. Patient files were reviewed for the following: patient age at start and end of therapy, interval from appearance of the lesion to start of therapy, duration of therapy, dosage, treatment completion or early discontinuation, clinical appearance after treatment, and side effects of treatment.

All patients underwent pretreatment evaluation by a pediatric dermatologist (D.B.A. or A.Z.). The dermatological evaluations included the extent, size, color, and firmness of the lesion. The findings on presentation were retrospectively grouped into two categories:

- Advanced lesions (group 1): hemangiomas of the nasal tip involving the subcutaneous tissue, leading to a visible disfigurement of the nasal tip.
- Limited lesions (group 2): superficial hemangiomas of the nasal tip, affecting only the nasal skin, measuring not more than 2 cm in greatest diameter, with no visible alteration of the nasal contour.

Prior to initiation of treatment, all patients underwent evaluation including cardiologic examination, electrocardiography, and echocardiography to rule out cardiac contraindications for propranolol treatment. Parents of the patients were provided with detailed explanation of the lesion, the treatment plan, and potential side effects of the drug, including but not limited to bradycardia, hypotension, bronchoconstriction, and reduced physiological responses to hypoglycemia. Propranolol was provided as an oral solution (Syprol, 5 mg/5 ml; Rosemont Pharmaceuticals Ltd.), or prepared from tablets to a suitable solution, at a starting dose of 0.5 mg/kg/day, in 3 divided doses. For the first 3 days of treatment, the drug was administered under supervision either in an inpatient ward or in the hospital day unit. The dose was incrementally increased to 2 mg/kg/day in 2 divided doses. Blood pressure, heart rate, and blood glucose levels were monitored during these 3 days. Treatment was continued at home; parents were instructed to monitor for side effects and to contact the physicians with any symptoms. Patients were evaluated once a month by a pediatric dermatologist. The dose was adjusted at every weight increase of 0.5 kg, evaluated monthly. In young infants, propranolol was continued until the age of 14–16 months and in older infants as long as there was still clinically evident regression of the hemangioma, unless side effects precluded its continued use.

The final therapeutic outcome was evaluated clinically and classified into the following categories:
- Very good: no visible residual lesion, normal shape of the nose.
- Good: near-normal shape of the nose, with or without visible residual lesion or scars.
- Partial: significant improvement from pretreatment appearance, with clearly visible residual lesion or scars.
- Unsatisfactory: no improvement (or ongoing significant aesthetic or functional impairment with need for correction).

Results

A total of 10 infants (4 male, 6 female) were included in the study. Their characteristics are shown in table 1. The mean age at referral to our clinic was 5.0 ± 5.3 months (range 1–18 months). Five cases were classified according to the study criteria as advanced lesions (group 1; 50%) and 5 as limited lesions (group 2; 50%). One patient (10%) was treated with corticosteroids and pulse dye laser before propranolol. The mean age at treatment initiation was 6.3 ± 6.2 months (range 2–22 months), and the mean interval from referral to start of therapy was 2.9 ± 6.1 months (range 0–20 months). The mean duration of treatment was 9.7 ± 3.3 months (range 5–13 months), and the range of follow-up after cessation of therapy was 6–10 months.

All patients were treated with propranolol syrup at doses of 2 mg/kg/day, with dose escalation and observation as described in the materials and methods. One patient (10%) developed wheezing, requiring discontinuation of treatment. The patient did not have known asthma prior to treatment. Nasal passage and airway obstruction due to hemangioma was ruled out by endoscopic examination by an otorhinolaryngologist. The wheezing resolved upon discontinuation of treatment and did not require hospitalization. Three patients had sleep disturbances (30%), manifested as night sleep arousing and crying; these did not necessitate dose reduction. There were no abnormal findings on monitoring of blood pressure, pulse rate, or blood glucose.

DOI: 10.1159/000346331
Clinical improvement was graded as ‘good’ in 8 patients (80%) and ‘partial’ in 2 (20%). Four of the 5 patients in group 1 (advanced lesions) had ‘good’ response, as did 4 of the 5 patients in group 2 (limited lesions). The hemangiomas became lighter in color and softer, with reduction in lesion diameter and thickness. These parameters continued to improve until the end of treatment. Treatment was stopped when the lesions were flat or had mostly resolved, with only mild residual skin color changes or residual telangiectasia. The observed improvement was maintained after cessation of treatment throughout the follow-up period. Representative examples from groups 1 and 2 are presented in figures 1 and 2.

Table 1. Clinical characteristics of the 10 patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Age at referral, months</th>
<th>Previous treatments</th>
<th>Age at propranolol initiation, months</th>
<th>Treatment duration, months</th>
<th>Side effects</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 (advanced lesions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>female</td>
<td>2</td>
<td>corticosteroids,</td>
<td>22</td>
<td>6</td>
<td>sleep disturbance</td>
<td>good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pulsed dye laser</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>female</td>
<td>3</td>
<td>none</td>
<td>4</td>
<td>11</td>
<td>sleep disturbance</td>
<td>good</td>
</tr>
<tr>
<td>3</td>
<td>female</td>
<td>2</td>
<td>none</td>
<td>2</td>
<td>12.5</td>
<td>sleep disturbance</td>
<td>good</td>
</tr>
<tr>
<td>4</td>
<td>male</td>
<td>2.5</td>
<td>none</td>
<td>3</td>
<td>11</td>
<td>–</td>
<td>good</td>
</tr>
<tr>
<td>5</td>
<td>male</td>
<td>8</td>
<td>none</td>
<td>8.5</td>
<td>8</td>
<td>–</td>
<td>partial</td>
</tr>
<tr>
<td><strong>Group 2 (limited lesions)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>female</td>
<td>2</td>
<td>none</td>
<td>3</td>
<td>4.5</td>
<td>wheezing, stop</td>
<td>partial</td>
</tr>
<tr>
<td>7</td>
<td>female</td>
<td>2.5</td>
<td>none</td>
<td>3</td>
<td>13</td>
<td>–</td>
<td>good</td>
</tr>
<tr>
<td>8</td>
<td>female</td>
<td>1</td>
<td>none</td>
<td>2</td>
<td>13</td>
<td>sleep disturbance</td>
<td>good</td>
</tr>
<tr>
<td>9</td>
<td>male</td>
<td>18</td>
<td>none</td>
<td>21</td>
<td>5</td>
<td>–</td>
<td>good</td>
</tr>
<tr>
<td>10</td>
<td>male</td>
<td>8.5</td>
<td>none</td>
<td>10</td>
<td>9</td>
<td>–</td>
<td>good</td>
</tr>
</tbody>
</table>
No discernable correlations in treatment response were seen with age at referral, age at initiation of treatment, or gender. Group 1 (advanced) lesions were treated for a mean of 10.6 ± 1.9 months, whereas group 2 (limited) lesions were treated for a mean of 8.9 ± 4.1 months. When only ‘good’ responders were included in the analysis (i.e. excluding partial responders), group 1 (advanced) lesions were treated for a mean of 11.5 ± 0.9 months, whereas group 2 (limited) lesions were treated for a mean of 10 ± 3.8 months.

Discussion

Nasal tip hemangiomas are associated with poor outcome, permanent disfigurement, and long-term adverse psychological consequences [1]. During the proliferative phase, children with nasal tip hemangiomas may have functional problems associated with nasal obstruction, alteration of the nasal valve, and destruction of nasal columella and septum; furthermore, the proliferating hemangioma may cause bleeding, ulceration, and pain. Although some authors have stated that nasal hemangiomas involute at the same rate as hemangiomas in other locations, other authors have commented that nasal tip hemangiomas involute to a lesser extent than other hemangiomas [13–17].

Corticosteroids have been used to treat problematic infantile hemangiomas for decades [18]. The risks of prolonged high-dose steroid therapy are well known, and this treatment has therefore been reserved for hemangiomas which are symptomatic or whose location or size suggests a particularly dangerous natural history [19]. However, other methods of treating hemangiomas, including a variety of vascular lasers and surgical approaches, have proven to offer limited benefit [20]. There is debate regarding the surgical approach. In 1979, Thomson and Langan [20] concluded that the conservative ‘no-touch’ approach is the best management of nasal tip hemangiomas since surgical outcomes resulted in poor aesthetic acceptability despite many revisions. However, recent literature supports external rhinoplasty approach.

Given the difficulty in treating hemangiomas, the 2008 report of propranolol benefits and the subsequent supporting reports have created a rapid and profound impact on the approach to treatment of both proliferative and late-phase hemangiomas [11, 12]. Propranolol has a well-documented safety and side-effect profile in children, where it has been used for cardiovascular indications for 4 decades. The mechanism of action of propranolol in the response of hemangiomas is poorly understood. No prospective, randomized, controlled studies have been performed to look at dosing or efficacy. The generally recommended dose is 2 mg/kg/day, given in divided doses.

Eivazi et al. [21] recently classified nasal tip hemangiomas as ‘limited’ or ‘advanced’ lesions. There is debate as to whether limited lesions should be treated. Proponents of early therapeutic intervention for limited lesions assert that early intervention may prevent further damage by proliferation of the hemangiomas [7]. Overall, 5 infants with limited lesions were included in this study. The infants with advanced and limited lesions responded similarly: both groups exhibited good response in 80% of patients. The duration of treatment was slightly longer (1.5 months) in advanced lesions.

The response rate of nasal tip hemangiomas observed in these children is similar to that seen in prior studies: nearly all patients respond, and those few who do not respond can be identified within the first few weeks of treatment. Bagazgoitia et al. [22] studied the response of hemangiomas at all body sites and noted a range of treatment response times, with most of the clinical response evident within the first 20 weeks of treatment. Within their subgroup analysis, hemangiomas of the nasal region responded slightly less than other facial hemangiomas. In our study protocol, treatment was maintained until full response was seen or until the lesion appeared to be static despite continued treatment. With this approach, the mean treatment time was slightly longer (9.7 ± 3.3 months, range 5–13 months) than that reported by Bagazgoitia et al. [22] for all body sites (clinical response judged as 50% or more was observed in 59% of patients at 16 weeks, with 21% of patients requiring treatment of over 32 weeks, or 8 months). This may reflect that a slightly longer treatment time is needed for nasal tip hemangiomas, which would be reinforced by the last data point in the analysis of Bagazgoitia et al. [22], wherein the response rate of nasal hemangiomas matched those of other facial hemangiomas at time points of 28–32 weeks (7–8 months). However, in their follow-up analysis, a recurrence rate was observed in 16% of patients at a follow-up of 0–6 months; we did not observe any recurrence, with follow-up of 6–10 months [23]. This might be explained by the longer treatment course that was used in our patients. Indeed, our mean treatment time of 9.7 months is similar to the treatment time reported by Price et al. [24], whose mean treatment duration was 7.9 months (for hemangiomas of all body sites) and whose recurrence rate was 3%.

No serious adverse events were observed in our group. However, Cavelli et al. [25] recently reported a case of a
1-month-old infant who developed hyperkalemia and hyperphosphatemia 24 h after starting propranolol therapy. The infant was diagnosed as tumor lysis syndrome. Parallel to the involution of the hemangioma, with continuation of the treatment, serum electrolyte levels returned to within normal level.

Our study clearly demonstrates that propranolol effectively reduces the size of nasal tip hemangiomas with minimal side effects. In patients with partial improvement, the partial response should still be considered a success given the high risks and low response rate associated with other therapies for this challenging type of hemangioma. Longer treatment times may be associated with lower recurrence rates, though further studies will be needed to develop a firm relationship between treatment time and recurrence rate. Given the high response rate and safety profile of propranolol, we concur that propranolol should be first-line therapy for the treatment of infantile nasal tip hemangiomas.

Disclosure Statement

The authors have no conflict of interest to declare.

References


