Review the experience: role of propranolol in infantile hemangioma (IHs) on pediatric patient

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Received: 30 April 2018
Accepted: 26 May 2018

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ABSTRACT

Background: Although not being licensed for the treatment of infantile hemangiomas (IHs) on pediatric patient 5 weeks or older than 5 months, propranolol is often used in these age groups to prevent or to treat potentially severe complications. The objective of the present study was to review the experience on pediatric patients with efficacy and adverse effects after use of oral propranolol treatment for IHs started before 5 weeks or after 5 months of age.

Methods: This was an observational study performed pediatric patients with IHs treated with oral propranolol at the department of pediatric surgery, Gandhi Medical College and Associated Kamla Nehru Hospital, Bhopal from Nov 2012-Nov 2014. Using a proforma, data was collected on dosing, efficacy and adverse effects.

Results: A total 40 patient of IHs from 2 months to 3yr were included in this study. The majority of patients were ≤6month of age 24 (60%) patient and 16 (40%) patients were >6month of age. Female 28 (70%) are more affected than male 12 (30%). The IHs most common lesion was 23 (57.5%) in head, face and nose region. No adverse effects were observed in our series; none of our patients had symptoms of hypoglycemia or hypotension. The patients with clinically significant more than 50% volume reduction were found in 26 (65%) patient and 25-50% volume reduction were found 14 (35%) patient after 5months long propranolol therapy for IHs.

Conclusions: In present study of patients propranolol 2mg/kg/day divided into two doses was a well-tolerated and effective treatment of IHs. Propranolol is clinically more effective treatment with no adverse effect and cost effective. The percentage of regression of size and color clearance was sufficient to justify the use of propranolol as the first line option for treatment of IHs.

Keywords: Infantile Hemangioma (IHs), Pediatric, Propranolol

INTRODUCTION

Infantile hemangiomas (IHs) are common benign and usually self-involution tumor (swelling or growth) of the endothelial-like cells or affect approximately 1 in 10 children. They tend to follow a natural course of rapid proliferation during the first year of life and subsequently regress over 5-10 years.1

The period and rate of growth are variable; some infants will have hemangiomas that grow very little, whereas others grow rapidly and at an unpredictable rate. Although most are not worrisome, ∼12% of IHs are significantly complex, requiring referral to specialists for consideration of treatment.2,3

Complications of hemangiomas, for which systemic pharmacotherapy is typically initiated, include permanent disfigurement, ulceration, bleeding, visual compromise, airway obstruction, congestive heart failure and, rarely, death. Despite the relative frequency of IHs and the
potential severity of complications, uniform guidelines for treatment are lacking.

Most haemangiomas are non-problematic, but a few become problematic, through ocular, airway or functional impairment, or ulceration. There are no US Food and Drug Administration (FDA)-approved agents for the treatment of IHs, and treatment is currently based on expert opinion and observational studies.

Prospective data addressing the efficacy and safety of any pharmacologic interventions for the treatment of IHs have not been generated, and available data are confounded by the lack of a consensus on treatment criteria and objective outcome measures.

Agents with reported activity in treating IHs include corticosteroids, interferon-α, vinca alkaloids, and, recently, propranolol. Oral propranolol therapy has been observed to inhibit the proliferation and incite regression of these lesions during their proliferative phase.

At present there are no nationally agreed guidelines on propranolol use in pediatric patients with IHs. In this study we assessed the efficacy and adverse effects of oral propranolol after use in IHs on pediatric patients.

**METHODS**

**Study design**

This was an observational study performed pediatric patients with IHs treated with oral propranolol at the department of pediatric surgery, Gandhi Medical College and Associated Kamla Nehru Hospital, Bhopal from November 2012 to November 2014. A proforma was used to collect information on patient demographics, indication for propranolol, dosing regimen undertaken, and observed outcomes.

**Patient monitoring**

During treatment with oral propranolol volume of IHs measured by size (length and width) was direct measured with flexible rubber tap and depth is measured by color doppler and compare during treatment at 15 days, 1 month, 2 month, 3 month, 4 month, 5 month and observe the reduction the volume in this period. Status of the patients of IHs by pulse rate during pre and post treatment follow-up was measured.

Treatment benefit was measured by subjective assessment of lesion regression by the medical team at clinic review. Improvement was documented objectively by serial photography by the medical photography department, providing a permanent record for parents and staff of the improvement in size, shape, colour, contour and residual deformity of lesions. Outcome of airway lesions was observed by appearance of haemangioma at repeat bronchoscopy.

**Dosage and duration**

Propranolol was given at a starting dose of 2mg/kg/day, in two divided doses a useful treatment for severe or complicated IHs, achieving a rapid and significant reduction in their size, this reduction was mainly achieved during the first 20 weeks of treatment.

**Severity scoring system**

A photograph-based severity scoring scale was used. Frontal and lateral pictures of every patient were taken before treatment and at every follow-up visit.

**Statistically analysis**

Statistical analyses were performed for quantitative variables; such as age and gender or time since the long propranolol therapy for IHs. The association with IHs most common region was categorical variables were presented as the number of cases and the percentage.

**RESULTS**

A total 40 patient of IHs were included in this study for analysis. The age of the patient is from 2 month to 3yr, were included in this study. The majority of patients were ≤6month of age 24(60%) patient and 16(40%) patients were >6month of age.

**Table 1: Summary of patient characteristics.**

<table>
<thead>
<tr>
<th>Categories</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12(30%)</td>
</tr>
<tr>
<td>Female</td>
<td>28(70%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;6 month</td>
<td>24(60%)</td>
</tr>
<tr>
<td>≥6 month</td>
<td>16(40%)</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
</tr>
<tr>
<td>Face</td>
<td>15(37.5%)</td>
</tr>
<tr>
<td>Nose</td>
<td>2(5%)</td>
</tr>
<tr>
<td>Head</td>
<td>6(15%)</td>
</tr>
<tr>
<td>Limb</td>
<td>10(25%)</td>
</tr>
<tr>
<td>Trunk</td>
<td>3(7.5%)</td>
</tr>
<tr>
<td>Anogenital</td>
<td>4(10%)</td>
</tr>
<tr>
<td><strong>Volume Reduction</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>26(65%)</td>
</tr>
<tr>
<td>25-50%</td>
<td>14(35%)</td>
</tr>
</tbody>
</table>

Female 28(70%) are more affected than male 12(30%). The most of 23 (57.5%) lesion were located in head face, nose and 10(25%) lesion located at limb,4(10%) lesion located at anogenital region and 3(7.5%) lesion located in trunk, so site of the IHs most common in head, face and
nose region (Table 1). No adverse effects were observed in our series; none of our patients had symptoms of hypoglycemia or hypotension.

Change of plus rate and blood glucose after use of propranolol in IHs are presented in Table 2.

Table 2: Bradycardia and hypoglycemia after use of propranolol in IHs.

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment (Mean)</th>
<th>After Treatment (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15d</td>
<td>1m</td>
</tr>
<tr>
<td>Pulse Rate</td>
<td>110±7.9</td>
<td>102±8.0</td>
</tr>
<tr>
<td>Blood Glucose</td>
<td>114±5.2</td>
<td>136±7.8</td>
</tr>
</tbody>
</table>

The patients with clinically significant more than 50% volume reduction were found in 26(65%) patient and 25-50% volume reduction were found 14(35%) patient after 5months long propranolol therapy for IHs. Scatter plot of length, width and depth of lesions before and after propranolol treatment during month and observe the reduction the volume in this period showed in Figure 1, 2 and 3. Repeat measurement and/or serial photography of hemangioma assessment of change in size and color, decrease in ulceration and inflammation of 6 months old male baby affected the left chest were showed in Figure 4.

Figure 1: Scatterplot of length of lesions before and after treatment.

![Figure 1: Scatterplot of length of lesions before and after treatment.](image1)

Figure 2: Scatterplot of width of lesions before and after treatment.

![Figure 2: Scatterplot of width of lesions before and after treatment.](image2)
DISCUSSION

Infantile hemangiomas (IHs) are the most common benign tumor in infancy. Although the majorities have little impact on childhood health, various problematic head and neck hemangiomas will develop rapidly and interfere with normal function and appearance. These problematic hemangiomas require intervention to control growth and reduce the likelihood of imminent functional and cosmetic deformities. Propranolol was recently found to lighten and reduce the size of hemangiomas during the proliferative phase of development.

Figure 3: Scatterplot of depth of lesions before and after treatment.

IHs is the most common infantile tumor, with a frequency of 4-10%. Recently, there has been an interest in propranolol and other beta-blockers in the treatment of IHs. Propranolol may be more effective and safer than previously established therapies and may be an alternative when more widely accepted treatments for IHs...
have failed. Initial studies suggest that it may also be used as a first-line therapy. Other selection criteria may include lesion location that is inaccessible to surgery, lesions with a deep component, severe ulceration and/or cosmetic disfigurement, obstruction of airway or visual axis, and the presence of contraindications to other medical therapies. Parental apprehension remains an important indication for treatment in cutaneous IHs.

Propranolol is a nonselective beta blocker that blocks the action of adrenaline of both beta 1 and beta 2 adrenergic receptor Léauté-Labrèze et al reported the effectiveness of propranolol for the treatment of IHs, more than 200 articles have been published regarding this form of therapy the vast majority reporting positive results. In present study of patients confirms that propranolol 2mg/kg/day divided into 2 dose a useful treatment for severe or complicated IHs, achieving a rapid and significant reduction in their size, this reduction was mainly achieved during the first 20 weeks of treatment .In this dose regimen significant reduction of IHs, this dose was maintained during the whole period of study. According to increased weight, change the dose of propranolol and found significant reduction of size of IHs. Authors generally advise that propranolol should be given with foods to reduce the risk of hypoglycemia and to withhold treatment if the child is vomiting or unwell. According to Bagazgoitia et al, seventy one patients confirms that propranolol 2mg/kg /day is a useful treatment for severe or complicated IHs, achieving a rapid and significant reduction in their size. This reduction was mainly achieved during the first 20 weeks of treatment. Manunza et al dose of 2mg/kg/day is effective in promoting regression and reduction morbidity from problematic cutaneous IHs. A higher dose of 3mg/kg/day has been used in Alderhey hospital and has been to be effective and well tolerated. Sánchez-Carpintero et al dose regimens have varied from series to series. Most have called for 1 to 3mg/kg/d of propranolol divided into 3 doses.

The demographics in present small patient population demonstrated characteristics that were consistent with the literature Manunza et al briefly described their experience with propranolol in 30 infants with hemangioma between July 2008 and April 2009, the average patient’s age at the start of therapy was 5.8 month (range 1.2-13.5 month). In present study of 40 patients, the average age of patient at the start of therapy was 8.8 months 24 patients were less than 6 month of age that is 60% patients less than six month of age and 16 patients were more than 6 month of age that is 40% patients more than six month of age. Zaher et al showed female infants are suffering from infantile hemangioma three to four folds more than male infants. Premature and low birth weight infants are more at risk of haemangiomas. IHs is developed in premature neonates 30% versus 5-10% of all infants. In present study IHs more common in female than male and ratio was 3:2. Twenty-eight female that is, 70% of female patient suffering from IHs and 12 male patients that is, 20% of male suffering from IHs.

Regarding regression of tumor IHs it is very important to measure the percentage of regression. In present study during treatment with oral propranolol can be measure the volume of infantile haemangioma size (length and width) was measured with soft flexible measuring tape and depth is measured by color doppler. Overall regression was seen in all patients that is 100% (n=40) during different follow up of treatment. 26(65%) patients more than 50% volume reduction after 5month long propranolol therapy for IHs. Fourteen (35%) patients 25-50% volume reduction after 5month long propranolol therapy for IHs. Zaher et al, reported 80% (24/30) with good or excellent response, defined as >50% improvement. Price et al, reported that 82% (56/68) of patients had at least 75% clearance of their IHs. Talaat et al, reported 75% (60/80) of patients with >75% clearance and 94% (75/80) with >50% clearance of their IHs. Bertrand et al reported two studies, one with 100% (12/12) of patients with >50% improvement and another with 97% (34/35) of patients with clearance between 25% and 75% with propranolol.

Until recently, the most common approach for patients with IHs in the post-proliferative phase was active non-intervention. In present series, propranolol improved esthetics in all patients, giving scope for more conservative surgical intervention in the future if necessary. These findings are consistent with those reported by Zvulunov et al, Schupp et al and Celik et al, who reported the results of propranolol therapy for hemangiomas beyond the proliferative phase, and imply that oral propranolol therapy may be warranted in children with late residual infantile hemangiomas, prior to any surgical intervention. Still, the most impressive responses occurred in the youngest patients, a finding that is consistent with the natural history of hemangioma, in which 80% of its size is reached by six months of age, and justifies referring such cases earlier for optimal therapeutic response.

The appropriate monitoring protocol for assessment of adverse effects in infants with IHs, before and during propranolol treatment, has not been established. The potential side effects of beta-blockers, which are well known and include bradycardia, hypotension, and hypoglycemia, must be borne in mind. Propranolol is also contraindicated in patients with asthma, and it is not recommended during episodes of bronchilitis. Marqueling et al, most concerning side effects of propranolol is symptomatic hypoglycemia which was noted in four patients, one of whom developed hypoglycemic seizure, patients on propranolol are at risk for hypoglycemia during prolonged periods of fasting or poor oral intake. Not withstanding propranolol appears to be a safe drug when correctly administered. No adverse effects were observed in present series; none of present patients had symptoms of hypoglycemia or
hypotension. However, until larger clinical trials are completed, potential adverse events should be borne in mind and consultation with local specialists such as pediatric cardiologists are recommended prior to initiating treatment.

CONCLUSION

In present study of patients propranolol 2mg/kg/day divided into two doses was a well-tolerated and effective treatment of IHs. Propranolol is clinically more effective treatment with minimum adverse effect and cost effective. The percentage of regression of size and color clearance was sufficient to justify the use of propranolol as the first line option for treatment of IHs. In present short series only one of the patients in whom propranolol was tapered showed a slight, non-significant, relapse, with no need to re-start treatment.

Propranolol can be tried as first line therapy in IHs irrespective of age, location, extent and phase of growth. Treatment is helpful in down grading the size and local complication of IHs. Due to the lack of long-term side effects of its high response rate, propranolol therapy may prove to superior to existing therapies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

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