Role of Propranolol in Management of Infantile Haemangioma: Our Experience
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ABSTRACT
Background: Infantile hemangiomas are the most common vascular tumors in infants and the most common benign soft-tissue tumors in infants and children with a prevalence of 4-10%. Most of the haemangiomas are self-resolving by the age of 7 years but few present as a challenge for management. Up to 30% require treatment like systemic corticosteroids, laser therapy, interferon-α, cryotherapy, embolization, radiotherapy, and intralesional sclerotherapy, all showing variable results. Since 2008 propranolol is effective in the management of challenging cases. At present, although many international and national studies have been done to evaluate different treatment modalities of infantile hemangioma, none is done in our local setups. Moreover, there is no specific agreed dose or guidelines for the use of propranolol in the management of infantile hemangioma for which our results can help.

Objective: This study aimed to evaluate the therapeutic effect of propranolol in the management of infantile hemangioma in our population to help in developing a proper dose regime with minimum adverse effects.

Materials And Methods: This prospective interventional study was conducted in the department of Pediatric surgery Bacha Khan Medical Complex, Swabi, Pakistan. The duration of the study was 26 months. After detailed history and investigation, the patients were started on a lower dose (1mg/kg/day in three divided doses) of propranolol and observed for six hours in the ward. After one week the dose was increased (2 mg/kg/day in three divided doses). The outcome was presented in terms of the percentage of regression of the mass as effective or non-effective.

Results: A total of 18 patients were treated with propranolol with a male to female ratio of 1:4. All patients tolerated the dose and had minimal side effects. All patients responded to the treatment with some early responders (n=16, 88.8%) while others responding late.

Conclusion: Our study showed that propranolol starting at a low dose after six months of age with gradually increasing it can have a good outcome with minimal side effects. Hence looking at its safety, we can say that propranolol can be given for small and non-problematic hemangiomas as well.

Keywords: Infantile Hemangioma, therapeutic effect, propranolol

INTRODUCTION
Hemangiomas are benign vascular tumors that must be differentiated from defects of vascular development which are not true neoplasms. These are soft and raised prominences on the skin, with a vivid crimson surface caused by an overgrowth of blood vessels in or under the skin. Hemangiomas follow a natural behavior with rapid growth during the first 6-12 months of life also known as the proliferative phase, followed by slow regression lasting up to 1-7 years of age also known as the involuting phase. Infantile hemangiomas are the most common vascular tumors in infants and the most common benign soft-tissue tumors in infants and children with a prevalence of 4-10%. Even though the prevalence is high, the majority of hemangiomas are benign and uncomplicated, with a small size, involuting spontaneously without requiring any intervention or treatment. Up to 30 percent of hemangiomas require treatment which is indicated for the larger, rapidly growing (particularly on the face, eyes, airway, or other cosmetic areas), and those presenting with pain, ulceration, secondary infection, bleeding, and/or tissue deformation.

Various treatment modalities have been identified for hemangiomas like systemic corticosteroids, laser therapy, interferon-α, cryotherapy, embolization, radiotherapy, and intralesional sclerotherapy, all showing variable results. Treatment with oral propranolol, i.e. a β-adrenergic receptor antagonist, has shown to inhibit the proliferation and encourage involution of these lesions in their proliferative phase. In 2008, a patient being treated for hypertrophic cardiomyopathy with propranolol was seen to have regression of the facial hemangioma. Since then, propranolol is being used as the first treatment option for haemangioma. Orally, 3 mg/kg/day for at least six months is the recommended dose of propranolol with good effect. Side effects include bradycardia, hypotension, bronchoconstriction, hypoglycemia, sleep disturbance, and gastrointestinal problems. At present, although many international and national studies have been done to evaluate different treatment modalities of infantile hemangioma, none is done in our local setups. Moreover, there is no specific agreed dose or guidelines for the use of...
propranolol in the management of infantile hemangioma for which our results can help. This study aims to present and share the experience regarding the therapeutic effect of propranolol in the management of infantile hemangioma in our population to help in developing a proper dose regime with minimum adverse effects.

**MATERIALS AND METHODS**

This prospective study was performed at the pediatric surgery unit of Bacha Khan Medical Complex, Swabi, Pakistan from 15th December 2017 to 14th February 2020 after taking ethical approval from its ethics committee. Patients of more than six months of age, large hemangiomas (>10mm), ulceration or bleeding, and functional or cosmetic impairment were put on propranolol and thus included in the study. The study was approved by the institutional review board (F.No:2-7/2017/GKMC/546-2).

Before starting on the therapy, a complete clinical examination of the respiratory and cardiovascular system was done. Investigations that include full blood count, blood sugar level, electrocardiogram, and echocardiogram were performed in all patients. Ultrasound of the abdomen was also performed for any concomitant intra-abdominal hemangioma. Oral propranolol was started with a dose of 1 mg/kg/day in three divided doses and they were observed for six hours after completing the regimen followed by discharge. On follow-up, the dose was gradually increased after one week to 2 mg/kg/day in three divided doses with continuation in the same dose until complete regression of the mass. A detailed proforma was made to collect demographic information, indication for therapy, dose and duration of therapy, and outcomes. Serial photography was used for documentation of improvement in color, shape, size, and any remaining deformity or a scar. Two patients with a scalp hemangioma before (and after four months of treatment with Propranolol (Figure 1) are shown.

![Fig 1. Two patients with haemangioma before and after 6 months of treatment with propranolol.](image)

The scale devised by Achauer et al. was used to assess the outcome as Grade I, 0-25% regression; Grade II, 26-50% regression; Grade III, 51-75% regression; and Grade IV, 76-100% regression. Results were compiled as effective for those responding to therapy with improvement i.e. Grade III and IV, while it was documented as non-effective for those not improving with therapy i.e. Grade I and II. The results were entered on Microsoft excel and calculated.

**RESULTS**

During the study duration, 18 patients had an indication for therapy, of which four (22.2%) were males and fourteen (77.8%) were females. Gender distribution according to different age groups is given in table 1.

All patients tolerated the initial dose and responded well to the treatment with sixteen of those showing effective results within six months of treatment while the remaining two showing a late response. Some patients are still under treatment for the complete regression but the improvement was visible within six months. The duration of propranolol treatment ranged from 5-24 months with a mean of 10.5 months. Some adverse reactions were observed as presented in table 2.

**DISCUSSION**

Oral propranolol can be used up to a dose of 8 mg/kg/day for the treatment of cardiovascular diseases. Our results showed that oral propranolol, when given up to 2 mg/kg/day, can be used safely for the treatment of infantile hemangioma and can fasten the regression of hemangiomas with very fewer complications. In this way, it can reduce the psychological effects on the parents. A study conducted by Léauté-Labrèze et al., Rosbe et al., and Holmes et al. showed that a dose of 3 mg/kg/day can also be
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Table 1: Age and gender distribution (n=18)

| Age               | Male (n=4) | Female (n=14) |
|-------------------|------------|---------------|
| 6-12 month        | 1          | 9             |
| 13-18 month       | 3          | 4             |
| >18 month         | 0          | 1             |

Table 2: Adverse effects of patients treated with propranolol (n=18)

| Adverse effects     | Frequency (%) |
|---------------------|---------------|
| Irritability        | 2 (11.1)      |
| Intermittent fatigue| 1 (5.5)       |
| Sleep changes       | 3 (16.7)      |
| Diarrhea            | 2 (11.1)      |

effective and well-tolerated.\textsuperscript{6,18,19} Since the socioeconomic conditions and the parents' education in our country is very poor, we gave lower doses to decrease the chances of potential complications and achieved encouraging results even on that dose.

Sixteen patients had visible regression in their mass early while two had a slow response. Even in those, the change was visible after a longer duration of treatment. Similarly, the high efficacy of propranolol has been observed in various studies like 90% success in a study in 31 hospitals of China.\textsuperscript{20} Moreover, a metanalysis by Lou et al. and a case series showed better results with propranolol when compared to other treatment modalities of infantile hemangiomas.\textsuperscript{18,21}

As seen in the available literature, a high female preponderance (4:1) was also noted in our results.\textsuperscript{22,23} Age at initiation of treatments conducted by Haider et al. and Tan et al. was early and in weeks but both of these studies were conducted in developed countries. We started the treatment mostly due to late presentation, possible reasons being the lack of parents education, awareness, and proper facilities for the observation and detection of early complications and their management.\textsuperscript{24,25} All patients are under follow-up for recurrence but so far no recurrence has occurred.

Complications of the treatment were very minimum and no serious complication was detected other than behavioral disturbances. This may be due to the higher age and lower doses at the beginning of the treatment, which may have sensitized the patient before starting on a higher maintenance dose.

Authors recommend that larger comparative studies and clinical trials should be done especially in our local and national setups so that a standard protocol can be generated for early recruit and management of all types of hemangiomas. As we observed very few adverse effects, this β-blocker can be tried and tested on smaller hemangiomas as well. Even the topical propranolol preparations can be tried for the superficial hemangiomas once those are available in Pakistan as it was done by Kunzi-Rapp.\textsuperscript{26}

We were limited by a smaller sample population collected from a single tertiary care pediatric surgery department even after extending the study duration to more than 2 years.

**CONCLUSION**

Treatment with propranolol is given for only the problematic haemangiomas and at low doses. But after seeing the safety of the oral drug, one can formulate criteria for the non-problematic haemangiomas as well. Topical propranolol preparations can be tried for the superficial haemangiomas once the topical preparation is available in Pakistan since studies have found these to be effective and safe. Our study concluded that oral propranolol is effective and safe when started in low doses with monitoring and gradually increasing to the target dose thus guidelines shall be developed for the national use.

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