Evaluation Of Role Of Propranolol In The Treatment Of Haemangiomas And Vascular Malformations

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Abstract: Introduction:Haemangiomas and arteriovenous malformations (AVM) aredifficult to classify and manage.The treatment of these lesions is individualized.Aims &Objectives:We evaluate the role of propranolol in the management of haemangiomas and vascular malformations.Methods& Material: All patients attending Plastic surgery OPD with resistant or difficult haemangiomas and vascular malformations of all ages were included in this study. The patients were started on oral propranolol in the dose of 0.2 mg/kg and gradually increased over a period of 1 week to 2 mg/kg given in 2 to 3 divided doses. Patients were reviewed weekly for the 1st two weeks and twice weekly for next 6 weeks and monthly thereafter on the basis of size of the lesion, colour of the lesion, consistency of the vascular anomaly.Results: 20 patients were included in our study - 9 patients with infantile haemangiomas, 6 patients with venous malformations and 5 patients with AVM.All 9 patients with haemangiomas had more than 25% reduction in the size of the lesion.Eleven of the 20 patients included in this study reported improvement in skin discoloration. Thus,haemangiomas had statistically significant benefit ($P<0.05$) with regards to change in size and skin discoloration whereas the results in vascular malformations were not statistically significant ($P>0.05$). There were no complications with propranolol at dose of 2mg/kg/day.Conclusion: Oral propranolol in the dose of 2 mg/ kg/day is an effective treatment modality for the infantile haemangiomas but not an effective treatment modality for the treatment of vascular malformations.. [Yogesh S SEAJCRR 2018; 7(4):1-8]

Key Words: Haemangioma, Venous malformation, Propranolol.

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Introduction: Hemangiomas and arteriovenous malformations are problems encountered frequently by plastic surgeons. The treatment of these is not straight forward and there are various options available for treatment ranging from topical creams to intralesional injections to systemic therapy, LASERs and surgical excision. However, none of these options have been universally accepted and their efficacy in all patients varies with the type of lesion.

The differentiation between hemangiomas and vascular malformations cannot be made on appearance alone as almost all vascular anomalies look similar. The old classification of vascular anomalies based on the appearance and histologic terms has been abandoned in favour of a new biological system based on clinical experience and corroborated by radiological and immunohistochemical studies[1, 2, 3].

Accurate diagnosis is possible for most vascular anomalies by correlating history and physical examination. Radiological evaluation is indicated in deep seated lesions. Imaging also confirms the flow rate and anatomic involvement. Biopsy is indicated whenever there is suspicion of malignancy.

Most haemangiomas don't require treatment and should be observed and their evolution explained to parents of the child [4, 5]. Approximately 10 % of hemangiomas require treatment as they are either causing obstruction of vital structure, distortion of involved tissues, impair functions of involved structures or complications like ulceration and repeated bleeding [6].

Treatment options for haemangiomas are intralesional steroids, systemic steroids, interferon alpha 2 A and vincristine used for steroid resistant lesions or surgical treatment for obstructive and deformative lesions [5, 7].

Vascular malformations are treated according to their individual types. Capillary malformation treated by laser or surgery. Lymphatic malformations treated mainly by sclerotherapy or surgery. Venous malformations are treated by sclerotherapy to decrease bulk followed by surgical excision. Arteriovenous malformation treated by embolisation or ligation of feeding vessels and surgical excision [5, 7].

A report has been made recently on the use of propranolol for infantile hemangiomas[4, 8]. The authors reported incidental decrease in the size of infantile hemangiomas on propranolol [4, 8]. This was tried only in infantile hemangiomas and regression was seen in most cases [8]. No such study has been done on Indian population till date.

The aim of this study was to see the effect of oral propranolol on size and colour of vascular malformations and hemangiomas.

Materials and Methods: This study was a prospective study carried out from August 2009 to October 2010. All patients attending Plastic surgery OPD with resistant or difficult hemangiomas and vascular malformations of all ages were included in the study. The vascular anomalies were classified according to location and size represented as percent of body surface area. All history of prior treatment for these vascular anomalies and details of the previous treatment were taken.

Patients were started on oral propranolol in the dose of 0.2 mg/ kg and gradually increased over a period of 1 week to 2 mg / kg given in 2 to 3 divided doses. Patients were reviewed every weekly for the 1st two weeks and twice weekly for the next 6 weeks and monthly thereafter.

The patients were assessed before starting therapy & at each follow up visit and following parameters assessed-size of the lesion, colour of the lesion, consistency of the vascular anomaly. Standard Clinical Photographs were taken prior to therapy and at each of the follow up visits to document the size reduction and colour improvement.

Valid Informed consent of the parent or the patient (if adult) taken after explaining about the nature and duration of the treatment and possible side effects.

Inclusion Criteria:

- Patients of all ages
- Patients with one or more hemangiomas sized more than 1 cm diameter
- Lesion not threatening for vital or functional structure

Exclusion Criteria:

- Alarming hemangioma (s) (complicated forms or localization at risk)
- Cardiac pathology (cardiac malformation, heart failure, cardiac arrhythmias, pulmonary hypertension)
- If the patient is a diagnosed case of
- Bronchial Asthma
- Bronchopulmonary dysplasia
- Bronchiolitis
- Raynaud syndrome
- Phéochromocytoma

Results:A total of 20 patients were included in our study. There were 9 patients with infantile hemangiomas, 6 patients with venous malformations and 5 patients with arteriovenous malformations. Thus, the number of patients with vascular (both venous and arteriovenous) malformations and hemangiomas were nearly equal (vascular malformations: 55%, hemangiomas: 45%). Majority of the patients in both groups were females (vascular malformations: 63.64%, hemangiomas: 77.78%).

All cases of vascular malformations were above 5 years of age. All cases of hemangiomas were less than 5 years of age with 7 being less than 1 year of age, i.e., they were in the proliferative phase (77.78%).

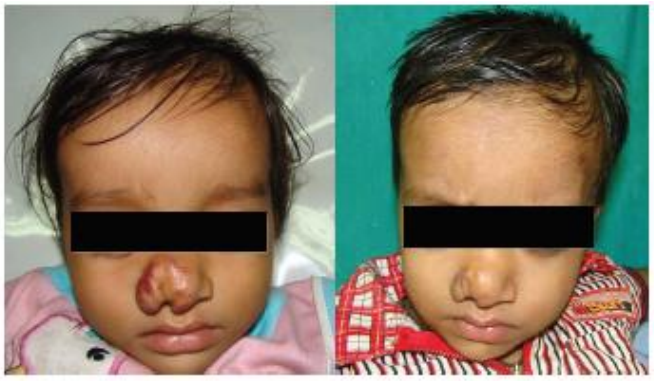
Majority of the cases of both groups had lesions in the head and neck region. Head and neck region was affected in 8 out of 9 patients with infantile hemangiomas; 3 out of 5 patients with arteriovenous malformations and in 3 out of 6 patients with venous malformations. Thus, total 14 patients had malformations in head and neck region.

Sixty-five percent of patients had received some form of treatment for their lesions elsewhere before presenting to us (hemangiomas: 23.08%, vascular malformations: 76.92%)

Eight of the 20 patients had functional impairment due to their lesion. Visual impairment and ulceration were the most commonly present impairments in 3 patients each.

14 of the 20 patients included in this study had reduction in the size of the lesion with treatment (Figures 1 and 2). All 9 patients with hemangiomas had more than 25% reduction in the size of the lesion ($P<0.05$) whereas all 5 patients with vascular malformations who had benefitted from this treatment reported less than 25% reduction in the size of the lesion ($P>0.05$) regardless of the duration of treatment (Figure 3 and 4).

Figure 1(a) and (b): Hemangioma nose - Pre therapy and post therapy showing decrease in size and colour.



Eleven of the 20 patients included in this study reported improvement in skin discoloration.

Figure 2(a) and (b):Hemangioma Cheek – Pre therapy and post therapy showing reduction in sizeand colour.

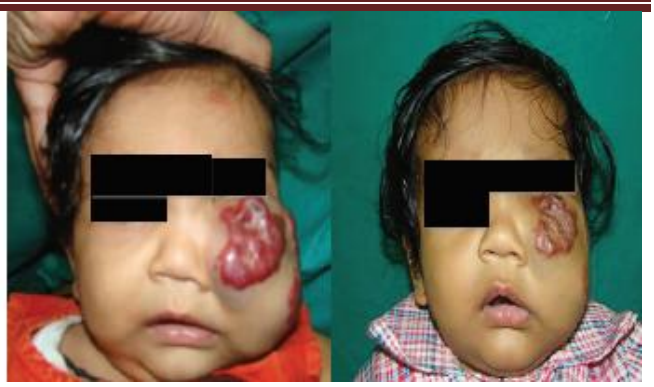


Figure 3 (a) and (b): Pre therapy and post therapy showing improvement in colour in venous malformation of tongue

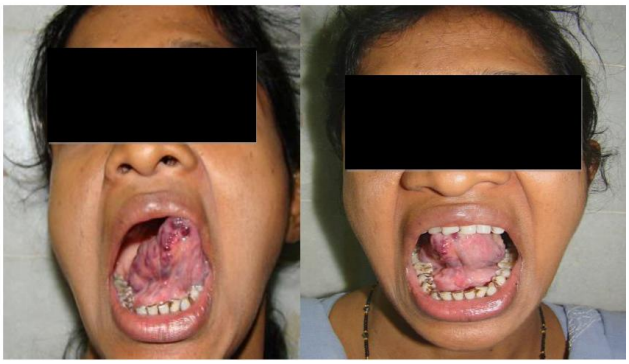
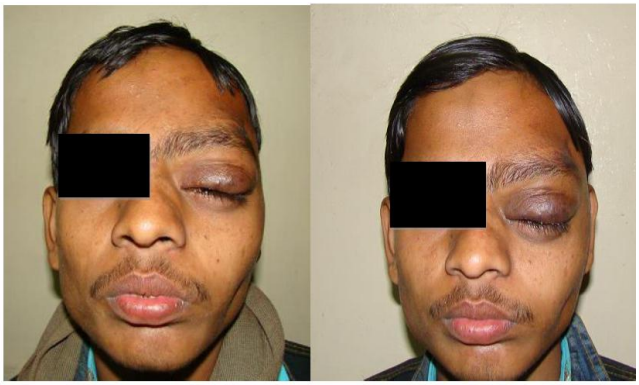


Figure 4(a) and (b): Pre therapy and post therapy Venous Malformation of orbit showing no increase / decrease in size.



All 9 patients with hemangiomas reported improvement in skin discoloration and only 2 of the vascular malformations reported a change in the skin discoloration regardless of duration of treatment**.** Thus,hemangiomas had statistically significant benefit ($P<0.05$) with regards to change in size and skin discoloration whereas the results in vascular malformations were not statistically

significant (P>0.05). There were no complications with propranolol taken at dose of 2mg / kg/ day.

Discussion: In 1982 Mulliken and Glowacki proposed the biological classification system for vascular malformations [3]. This system divides vascular anomalies into haemangioma, which are neoplastic lesions with endothelial hyperplasia, and vascular malformations, which are congenital lesions with normal endothelial turnover 9. Vascular malformations are further sub-classified by the predominant type of vessels found within the lesion (i.e., venous, arterial, lymphatic, capillary, or mixed) and upon blood flow within the lesion (i.e., high flow vs. low flow). It should be noted, however, that histologic and radiologic sub-classification can be difficult because of overlapping characteristics.

The biological classification system has proven very useful clinically in establishing a clear diagnosis and prognosis for vascular lesions, and has been shown to correlate well with angiographic, ultrasound, and magnetic resonance imaging (MRI) findings [2, 10, 11]. The increasingly wide-spread use of the biological classification system not only simplifies the diagnosis of these lesions, but facilitates precise communication between physicians, which is necessary for a multiple subspecialty team approach to patient treatment [1, 12].

Regulators of hemangioma growth and involution are poorly understood [8]. During the growth phase, two major proangiogenic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF); histologic studies have shown that both endothelial and interstitial cells are actively dividing in this phase [8]. During the involution phase, apoptosis has been shown. Potential explanations for the therapeutic effect of propranolol — a nonselective beta-blocker — on infantile capillary hemangiomas include vasoconstriction, which is immediately visible as a change in color, associated with a palpable softening of the hemangioma; decreased expression of VEGF and bFGF genes through the down-regulation of the RAF–mitogen-activated protein kinase pathway(which explains the progressive improvement of the hemangioma); and the triggering of apoptosis of capillary endothelial cells [8].

Recent studies have suggested the role of propranolol in infantile hemangiomas[8]. Before these studies, oral steroids were the mainstay for treatment of these lesions [13]. However, the main concern with this mode of therapy was the immunosuppression risk in these patients. To counter this intralesional and topical steroids were also used successfully for infantile hemangiomas[13].

Propranolol is as effective for the treatment of infantile hemangiomas as oral steroids with the added advantage of the absence of any chance of developing immunosuppression due to the therapy [4, 8, 14]. When compared with intralesional steroids the results of propranolol are better than intralesional or topical steroids with the added advantage of the therapy being non invasive.

Leutze et al suggested the role of propranolol in the treatment of infantile hemangiomas[4]. In all patients, 24 hours after the initiation of treatment, they observed a change in the hemangioma from intense red to purple; this change was associated with a palpable softening of the lesion. After these initial changes, the hemangiomas continued to improve until they were nearly flat, with residual skin telangiectasias. Ultrasound examinations in five patients showed an objective regression in thickness associated with an increase in the resistive index of vascularization of the hemangioma. Infantile capillary hemangiomas are composed of a complex mixture of clonal endothelial cells associated with pericytes, dendritic cells, and mast cells [4, 8].

In another follow up study done by the same authors 32 patients of infantile hemangiomas were studied [4, 8]. In all cases, informed consent was obtained from both parents. This was an observational study. They included all patients

with complicated IHs in need of treatment, according to the ad hoc American Academy of Dermatology Guidelines/Outcomes Committee. They excluded infants with cardiovascular disorders contraindicating propranolol use, after a pediatric cardiologist evaluation or a recent outbreak of wheezing [4].

In their study, the efficacy of propranolol reached 100%, with the first effects appearing in the first hours of treatment as changes in color and softening of the lesions [4, 8]. This rapidity of action was especially dramatic in cases involving dyspnea, hemodynamic compromise, or palpebral occlusion. Another remarkable aspect of the results of propranolol treatment is that, not only was IH growth stabilized (which often is achieved with corticosteroids), but the improvement continued until complete involution was achieved, which led to considerable shortening of the natural course of His [4, 8].

The same authors did a follow up study in which Propranolol was given to a total of 32 patients according to the following protocol [4]. At inclusion, a clinical evaluation with photographs and, when possible, an ultrasound examination (measuring the maximal thickness of the lesion and the resistivity index) were performed, together with electrocardiographic and echocardiographic evaluations to rule out treatment contraindications. Treatment was initiated during a short hospitalization of 24 hours or during a day hospital session. The drug was then given at a starting dose of 2 mg/kg per day, in 2 or 3 divided doses. For their first patients, propranolol was administered in 3 divided doses when the IH was particularly alarming, because of the concern about the short half-life of the drug (3 hours). In 4 cases, the initial dosage was 3 mg/kg per day to maximize efficacy, because of cardiac indications in 1 case, severe laryngeal dyspnea in 1 case, and painful ulcerations in 2 cases. They monitored blood pressure and heart rate every hour during the first 6 hours of treatment. In the absence of side effects, treatment was continued at home and the child was reevaluated after 10 days of treatment and then every month. Monthly evaluations consisted of clinical and photographic evaluations of the IH and monitoring of treatment compliance and tolerance (heart rate and blood pressure) [4].

Cheng JF et al performed a retrospective review of patientscollecting data on colour, size of lesion, duration of treatment and side-effects of propranolol treatment [14]. Main outcome measures were colour and size of infantile haemangioma before and after treatment, the change in astigmatism of our patients and the incidence of complications from propranolol. They reviewed 10 patients with infantile haemangioma. They were treated with propranolol oral syrup 2 mg/kg/day in divided doses for a mean duration of 32.8 (range 12-42) weeks. All patients had a reduction in colour and size of the lesions. The mean lesion size decreased from 756.7 to 543.2 mm(2) after treatment (P = 0.075). Five patients had significant astigmatism and 60% had successful reduction of astigmatism after treatment. Hence authors concluded that propranolol appears to be a safe and effective treatment in the management of infantile haemangioma [14].

Li YC et al had a case series of four patients with orbital infantile haemangiomas[15]. Two of the patients had inadequate responses to prior corticosteroid therapy. One of the patients was commenced on propranolol at 2.5 years of age when the lesion was not in the proliferative phase. The patients were treated with oral propranolol. All patients had significant improvement in their physical appearance, ocular examination findings and size of their lesions on radiological evaluation. Hence the authors concluded that propranolol is a promising treatment against infantile haemangiomas in the orbit, not only in infants but also in an older child with a stable lesion [15].

Holmes WJ et al prospectively assessed the efficacy of propranolol as a first line treatment for problematic haemangioma, and develop a

treatment regime [16]. 31 consecutive patients with rapidly proliferating infantile haemangioma with functional impairment or cosmetic disfigurement were treated with propranolol as a first line treatment. All patients had cardiovascular pre-treatment work-up and commenced on propranolol at 3mg/kg/day. A rapid halt in haemangioma proliferation was seen in 100% of patients and significant regression in 87% of patients. This treatment is well tolerated and has little side effects. Since this study, their unit has adopted the policy of using propranolol as a first line treatment for all problematic proliferative infantile haemangiomas[16].

Chik KK et al did a retrospective study in children 3 years old or younger with facial haemangioma who took oral propranolol between 1 December 2008 and 1 December 2009 [17].12 such patients studied, all of whom underwent prior clinical evaluation before starting the treatment. Ten patients had a solitary facial haemangioma and two had multiple haemangiomas. The mean age of symptom onset was 12 days. The mean age for starting propranolol treatment was 7 months, and in all cases a clinical response was observed within 7 days. Five (41%) of the patients had complete resolution 2 to 6 months after starting medication, at which time they were 5 to 12 months old. Two of them had a recurrence of the haemangioma within 8 weeks of stopping the drug, but responded to a second treatment course. In these two patients, the propranolol dosage had been tailed down rapidly and the therapy was of a shorter duration than in those without recurrence. The remaining seven patients were still taking propranolol and responding satisfactorily. Hence the authors concluded that propranolol was useful as first-line or single-agent treatment of facial infantile haemangioma in Chinese children, and gave rise to minimal side-effects. Although recurrence of infantile haemangioma occurred after propranolol was tailed off rapidly after a relatively short duration, an optimal treatment duration and tapering schedule has not yet been defined. Nevertheless, patients responded well to second courses of propranolol therapy [17].

Haider KM et al did retrospective, observational case series in patients with vision-threatening hemangiomas[18]. Outpatient, oral propranolol therapy was initiated between 3 weeks and 12 months of age. The dosage was slowly increased to 2 mg/kg daily over the course of 1-2 weeks. Response to therapy was deemed "excellent" (>50% reduction in size), "good" (decreased size but <50%), "fair" (no further growth), or "poor" (continued growth or intolerable adverse effects). A total of 17 patients were treated with oral therapy. Of these, 10 had excellent results, 6 had a good response, 1 fair, and none poor. Thus the authors concluded that outpatient propranolol treatment reduced the size or stopped the growth of all hemangiomas treated, with excellent response in more than half of all patients treated and only minor side effects [18].

In our study of 11 patients with vascular malformations treated with oral propranolol 5 patients had a poor response with < 25% reduction seen whereas no response was seen in 6 cases of vascular malformations ($P>0.05$) regardless of the duration of treatment. Only 2 of the vascular malformations reported a change in the skin discoloration regardless of duration of treatment.($P>0.05$) The original size of the vascular malformation had no significant correlation with the amount of reduction seen in both hemangiomas and vascular malformations ($P>0.05$).In our study no significant benefit was seen in patients with vascular malformations.

In cases with arteriovenous malformations embolisation followed by surgery is the mainstay of treatment [5, 7]. Whereas in cases with venous malformations, sclerotherapy and surgical debulking form the mainstay of treatment[5,7].Propranolol is not a very reliable and effective mode of treatment for such lesions [5, 7]; Especially when established modes of treatment for these lesions provide better and more reliable results for the treatment of these disorders.

The original size of the lesion has no significant correlation with the amount of reduction seen in both hemangiomas and vascular malformations (P>0.05). In this study 25 – 50% reduction in size of the lesion was seen in 5 cases with hemangiomas and 50 – 75 % reduction was seen in 4 cases of hemangiomas, thus all cases in our cases had good to excellent results after oral propranolol therapy. These results were similar to the results achieved by the pioneering studies done by Leaute – Labreze et al [4, 8.]

Few studies have reported complications like hypoglycemia and hypotension after propranolol [17, 18, 19, 20].Chik et al observed hypotension in two patients, one of whom tolerated a lower dose and in the other, therapy was reinitiated at her older age [17].Breur JM et al reported a case of hemangioma treated with propranolol who, developed symptomatic hypoglycemic events presumably because of a concurrent deficiency of epinephrine and cortisol as a direct result of both beta-blockage by propranolol and adrenal insufficiency as a result of prednisone use [18]. Authors concluded that extreme care should be taken in patients treated with both propranolol and prednisone as they are at increased risk of hypoglycemia[19].Holland KE et al reported the cases of 3 patients who developed symptomatic hypoglycemia during treatment with propranolol for their IHs [20].

Haider KM et al reported mild adverse effects in 6 of the 17 patients treated with propranolol and included the following: increased gastric reflux lasting 1 week, intermittent fatigue during the first 2 weeks, gastrointestinal upset, and slight "shakiness" with a missed dose [18.] However in their series, no symptoms were severe enough to discontinue treatment [18.]

However most studies have concluded that propranolol is a safe drug when used in a dose of 2 mg/ kg/ day for infantile hemangiomas[4, 8, 14, 15].

Conclusion: Oral propranolol in the dose of 2mg / kg / day is an effective treatment modality for the treatment of infantile hemangiomas as reduction in size and betterment of skin colour was seen in statistically significant number of cases.Also we deduced that oral propranolol is not an effective treatment modality for the treatment of vascular malformations as no statistically significant reduction in size or betterment of skin colour was seen.We recommend treatment of all cases of infantile hemangiomas with oral propranolol in the dosage of 2 mg/ kg /day for a treatment duration of 3 – 4 months.

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