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Original Article

Use of Propranolol for the management of haemangioma in children: Our experience

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Abstract:

Hemangioma is one of the most common benign tumors of infancy and occurs in approximately 5-10% of infants. The treatment options for problematic haemangioma are intralesional and systemic steroids, chemotherapeutic agents including vincristine and interferon-alpha, laser therapy or surgical intervention. In this case series effectiveness of propranolon was observed on haemangioma. This study was conducted in the Department of Pediatric Surgery, Faridpur Medical College Hospital, Faridpur and Shahid Ziaur Rahman Medical College, Bogra. This study period was from January 2013 to December 2015. A total of 38 patients of haemangioma were admitted in Pediatric Surgery ward in FMCH and 26 patients in SZRMCH. These 54 patients were counseled about the study in detail. First dose of propranolol was given at a dose of 3 mg/kg/day in three divided doses. Pulse and blood pressure were recorded during initial 3 hours. Patients were then advised to continue with this treatment at home, with monthly follow-up. Total number of patients were 54. Of them 11 were male and 43 were female, giving a male: female ratio of 1:4. 60 % of the patients (32) were in <6 months. After 1 month, sign of regression was marked in all cases. Complete regression was seen in 6 patients (11.1 %) during second follow-up after 3 months of treatment. Only 4 patient required 9 months to reach the complete recovery. This case series contributes to the growing evidence that oral propranolol is efficacious and safe, with a careful dosing and monitoring. We hope a national guidelines will be developed in time for use of propranolol to treat the haemangioma.

Key words: Haemangioma, Propranolol, Corticosteroid.

Introduction:

Hemangioma is one of the most common benign tumors of infancy and occurs in approximately 5-10% of infants[1]. The male to female ratio is variable with some reports suggesting the condition is up to four times more common in females[2]. It is more common in Caucasion and less common in Blacks.

At birth, hemangiomas may not be apparent or may appear as small flat circumscribed lesions with telangiectatic vessels on the surface. The cutaneous lesions present soon after birth and are characterised by rapid proliferation during the first year of life, followed by a gradual involution over the next five to ten years. Regression is complete in 60 % patients by the age of 4 years and in 76 % cases at 7 years[3]. Because of this benign, self-limited course, therapeutic treatment is not essential in most of the cases. Only 10 % of hemangiomas require treatment because of rapidity of growth, life-threatening locations, local complications, and cosmetic and functional risks. Hemangiomas may be life-threatening when they are present at the upper airways and liver and when they cause local complications such as hemorrhage, ulceration and necrosis leading to septicemia or disseminated intravascular coagulation.

The treatment options for problematic haemangioma are intralesional and systemic steroids, chemotherapeutic agents including vincristine and interferon-alpha, laser therapy or surgical intervention[4]. Propranolol is a non selective beta blocker. It is currently licensed for treatment of arrhythmia, hypertension, thyrotoxicosis in

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children and migraine prophylaxis[5,6]. In 2008 regression of a facial haemangioma was noted in a child being treated with propranolol for obstructive hypertrophic cardiomyopathy[7]. Since then propranolol has been introduced as a primary treatment for complicated haemangioma. The precise mechanism of action of propranolol on hemangiomas is not clear. Current theories include vasoconstriction, which is immediately visible as a change in color, associated with a palpable softening of the hemangiomas. Propranolol decreases 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.

Materials and Methods:

This study was conducted in the Department of Pediatric Surgery, Faridpur Medical College Hospital, Faridpur and Shahid Ziaur Rahman Medical College, Bogra. This study period was from January 2013 to December 2015.

All the patients admitted in Pediatric Surgery ward with rapidly growing hemangiomas, presented with local complications like ulcer or bleeding and/or had cosmetic or functional risks. Patients with cardiac pathology (cardiac malformation, heart failure, cardiac arrhythmias, pulmonary hypertension) and respiratory distress, asthma, bronchopulmonary dysplasia were not included in this study.

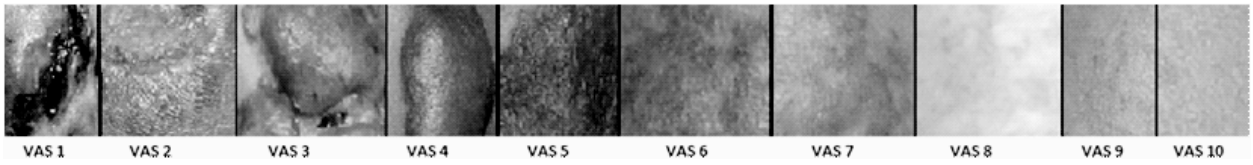

Fig 1: Visual Analog Scale (VAS) of ten segments.

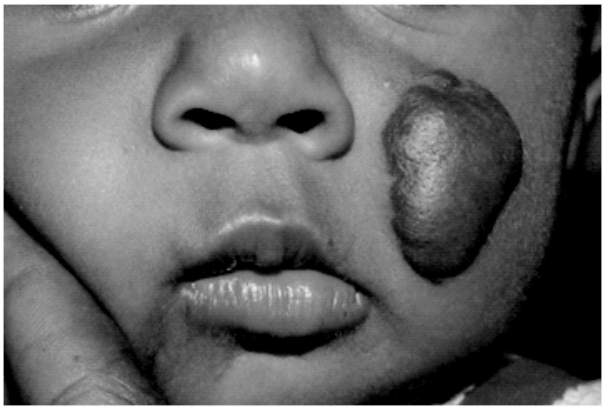

Fig 2a. The lesion on face prior to propranolol treatment.

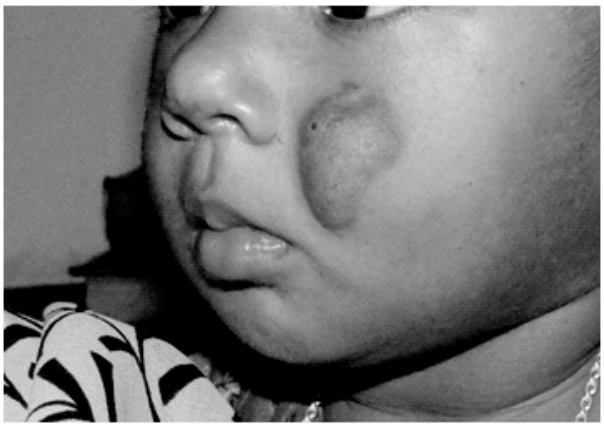

Fig 2c. 1 month after starting propranolol.

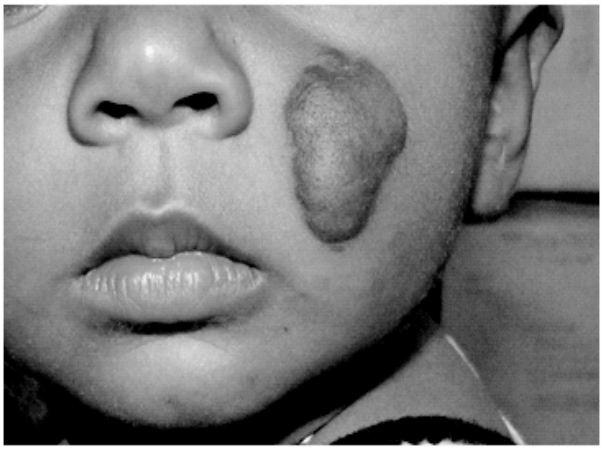

Fig 2b. 3 hour after starting propranolol.

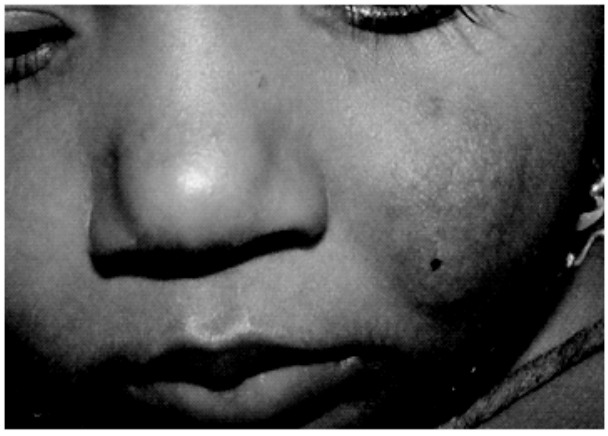

Fig 2d. 3 months after starting propranolol.

Pre-treatment screening investigations

* Full clinical examination including cardiovascular and respiratory assessment.
* Complete blood count.
* Thyroid function test.
* Abdominal Ultrasound (in patients with multiple lesions)
* Medical Photography

A total of 38 patients of hemangioma were admitted in Pediatric Surgery ward in FMCH and 26 patients in SZRMCH. These 54 patients were counseled about the study in detail. Written consent was obtained prior to data collection and taking photographs.

Results:

Total number of patients were 54. Of them 11 were male and 43 were female, giving a male: female ratio of 1:4. Range of age in this study was 1 month to 6 years with a mean of 25.75 month. 60 % of the patients (32) were in <6 months. Signs of stabilization were seen in all patients 100 % after 3 h of initiation of treatment, color of the lesion changed from red to purple and lesion became softer (VAS "5"). After 1 month, sign of regression was marked in all cases. Complete regression (VAS "9") was seen in 6 patients (11.1 %) during second follow-up after 3 months of treatment and other 21 patients reached VAS "9" months of treatment. Only 4 patient required 9 months to reach VAS "10" means the complete recovery.

Table I: Status of the patient of haemangiomas by visual analog scale (VAS) at post treatment follow-up.

Time	n	VAS 5 No (%)	VAS 6 No (%)	VAS 7 No (%)	VAS 8 No (%)	VAS 9 No (%)	VAS 10 No (%)
3 hour	54	54 (100)	0	0	0	0	0
1 month	54	0	42 (77.78)	08 (14.8)	04 (7.4)	0	0
3 months	54	0	0	17 (31.5)	31 (57.4)	06 (11.1)	0
6 months	21	0	0	0	05 (23.8)	13 (61.9)	04 (19.05)
9 months	04	0	0	0	0	03 (75)	01 (25)

First dose of propranolol was given at a dose of 3 mg/kg/day in three divided doses. Pulse and blood pressure were recorded during initial 3 hours. Patients were then advised to continue with this treatment at home, with monthly follow-up. Mobile phone number of the researcher was given to every patient and they were instructed to call with any query. Patients who did not turn up for scheduled follow ups were contacted on their cell phone. Photographs were taken before treatment, 3h after treatment had started and at each follow-up day in multiple points of view. Photographic record was kept for each patient's findings. Changes after treatment were measured on a visual analog scale (VAS). Pulse rate, blood pressure and complications were also recorded at every follow-up of the patients.

Photographs were evaluated according to VAS.

Visual analog Scale (VAS) (Fig. 1.)

1- Hemangioma with bleeding
2- Ulcerated hemangioma
3- For rapidly growing hemangioma
4- Slowly growing hemangioma
5- For static phage (signs of stabilization-red to purple color change and loss of shininess)
6- Signs of early regression (color from red to pink and reduced skin elevation)
7- Faded hemangioma
8- For more near normal skin color and slightly raised skin
9- Complete regression (skin stain and excess adipose tissue may present)
10- Complete cure.

At the end of the treatment hemangiomas were almost flat; in few cases deposition of excess adipose tissue and mild residual skin stain was seen. No relapse was observed in any of the cases.

Discussion:

Propranolol has been used for decades in the practice of paediatrics for the treatment of cardiovascular disease at a dose as high as 3mg/kg/day. The efficacy of propranolol in this study is 100 %. Every patients n= 54 (100 %) showed initial response of purple coloration of the lesion, diminished shininess and softening of the surface after 3 h from the start of medication (Fig. 2b). Results from our case series indicate that propranolol at a dose of 3mg/kg/day is effective in promoting regression and reducing morbidity from problematic cutaneous infantile haemangiomas.

This dose (2mg/kg/day) has been reported as effective in other centres[9]. A higher dose of 3mg/kg/day has been used in Alderhey Hospital, and has been shown to be effective and well tolerated[7].

On first follow-up after 1 month each and every patients showed signs of regression. 77.78 % (n = 42) was improved to VAS "6", other 8 patients to VAS "7" and 4 patients to VAS "8". Thus, sign of initial stabilization was seen in first few hours and sign of regression was marked in the first month of treatment which is the important aspect of management of

complicated hemangiomas. 100 % efficacy and similar pattern of responses were also seen in Sans et al[4,7].

A low incidence of side effects was reported in our patient group, namely disrupted sleep, lethargy and bradycardia. We wonder if the child with bradycardia was prone to this, given the underlying congenital hypothyroidism. Lethargy and sleep disturbance are recognised side effects of propranolol[8]. Well documented side effects not observed in our group but reported elsewhere include hypoglycaemia, gastrointestinal upset and bronchospasm[1].

The effect of propranolol on infantile haemangiomas was discovered incidentally and little is known about its precise mechanism of action in these tumours. The possible mechanisms include vasoconstriction, inhibition of angiogenesis and induction of apoptosis[9].

Propranolol is effective during the proliferative phase of growth. Patients who had a poor response to propranolol were those who were commenced on therapy at an older age. This highlights the need for prompt early referral of infants with problematic haemangiomas, for consideration of propranolol therapy. When started at the proliferative stage, the growth of the lesion is inhibited and regression promoted. It may be that the children who did not benefit from the therapy had passed this proliferative stage.

In Sans et al study, one patient had stopped propranolol during acute respiratory tract infection and restarted after the episode. One patient was noted for decreased blood pressure during sleep, resolved spontaneously when the child awoke; one child developed wheezing and needed to stop the treatment due to unrecognized allergic asthma[4]. In this study, there was no change in blood pressure in any of the subjects and no major bradycardia was found during the treatment period.

In 2012 Hasan M. et al shows 100% stabilization after 3 h of initiation of treatment, color of the lesion changed from red to purple and lesion became softer (VAS "5")[10]. Our study also correlates with this observation.

Conclusion:

This case series contributes to the growing evidence that oral propranolol is efficacious and safe, with a careful dosing and monitoring. We hope a national guidelines will be developed in time for use of propranolol to treat the haemangioma.

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