ORIGINAL ARTICLE

Oral Propranolol Therapy in the Management of Infantile Cutaneous Haemangiomas

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Abstract

Infantile Haemangiomas is one of the commonest childhood tumours. Several modes of treatment are available including observation only. Recently propranolol has been used as first line therapy in various reports. We present here a prospective study of 30 patients of Infantile Heamangiomas in which propranolol was used with an aim to study the dose standarization, efficacy & safety profile of the drug. All the patients had pretreatment cardiovascular , respiratory and investigative work up and then started on oral propranolol therapy at a dosage of 2-3mg/kg/day in two divided doses for a mean duration of 7.8 months (range 6-9 months). All the patients responded to the treatment by showing reduction in size, colour changes in the lesion and resolution of ulceration. In maximum 22 (73.33%) patients there was >50% reduction i size, 6(20%) patients had complete resolution of the lesion and only 2 (6.66%) had <25% reduction in size. All 4(100%) patients with ulceration had complete healing of the ulcer. There was no major side effect of the drug except mild self limiting diarrhoea in 2(6.66%) patients. We conclude that oral propranolol should be used as first line therapy in all infants with Infantile Cutaneous Haemangiomas at an early stage when response is good.

Keywords

Infantile Haemangiomas, Haemangioma, Propranolol, β-blocker

Introduction

Infantile Haemangiomas(IHs) are the most common soft tissue tumours of Infancy occurring in 1-4% of children under 1 year of age (1) with female to male predominance of 4:1(2). Majority of the lesions are located in the head and neck area 60%, followed by trunk 25% and extremities 15% (3,4).

Typically they are not present at birth or may appear as small flat circumscribed lesion at birth and then undergo rapid proliferation during Infancy followed by an involution phase over first few years (5). So, in majority of the cases treatment is not necessary and only strict follow up is

advised. However some of these lesions can have complications like infection and ulceration, massive growth, cosmetic disfigurement or impairment, impact on normal function(e.g periorbital, lip, external genitalia) and many of these leave behind permanent squealae with potential psychological effects in children and their parents (1,6). Therefore timely therapeutic intervention is usually needed even in uncomplicated cases (7). In literature tropical or oral corticosteroids have been used as first line therapy in rapidly growing

complicated IHs (8). Other modalities reported includes- nterferon á, vincristine, topical imiquimod, laser therapy or surgical excision (9). The efficacy of these modalities is variable and have associated side effects or even long term safety concerns (1,10,11).However in recent years propranolol, a non

selective â adrenergic blocker has emerged as first line therapy in the management of IHs. Since the initial report of Leaute-Labreze et.al in 2008(12), many studies have appeared in literature showing the usefullness, efficacy and safety profile of oral propranolol for the treatment of IHs at an early stage (13).

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Here in we present a prospective study of 30 patients of IHs treated with oral propranolol at a dose of 2-3mg/kg/day conducted at our centre for the first time to evaluate the dosage standardization, efficacy and safety profile of the drug in early management of these lesions.

Material and Methods

The study was conducted in the Department of General Surgery (Paediatric Surgical Division) Govt. Medical College Jammu over a period of 1 year Duration from November 2015 to October 2016. All the patients of IHs involving various parts of body in age group of 1month to 12 months of either

sex were included. Various indications for starting early treatment were disfiguring lesions of head and neck area, multiple lesions, functionally threatening lesions of limbs, genitalia and natural orifices. After the initial clinical evaluation by a senior paediatrician which included general physical

examination, cardiovascular and respiratory evaluation, ECG, Ultrasound abdomen, laboratory investigations like complete blood count, blood sugar levels and liver function tests, following patients were excluded from the study-infants with cardiac anomalies and arrhythmias, bronchospasm, known hypoglycaemia, liver failure and prematurity. Treatment was initiated during hospitalization for a period of 72 hours. At presentation each lesions was evaluated for site, size, colour, consistency, maximum diameter in two axis and clinical photographs with 5 pixel digital camera at 30 cm distance and 2mb resolution. Clinical assessment with measurements and photograph was repeated after 72 hours, 1 week, 2 week, monthly for 3 months, 6 months and subsequently depending upon response to therapy. Since oral liquid form of Propranolol is not yet available, the tablet formulation was crushed and suspension was made in water/milk with addition of sugar or honey to make it more palatable. Propranolol was given with a starting dose of 1mg/kg/day in two equal divided doses and if tolerated well, increased to 2mg/kg/day within a week period. In case of adequate response with no major side effect, the drug was continued at a dose of 2mg/kg/day in two divided doses and was adjusted for weight increase on each follow up. In those patients who did not show significant response within first 3 weeks and also in cases of large size and complicated ulcerated lesion, the dosage was increased to 3mg/kg/day in two equally divided doses. The treatment was continued over a period, varying between 6 months to 9 months or until early complete resolution occurred. Therapy was tapered over a period of 1 month in the end & patients continued in follow up to look for the relapse. At the completion of the treatment various parameters were recorded for appropriate statistical analysis.

Results

Thirty patients who met the inclusion criteria were enrolled for the study. Mean age of the patients at the beginning of the study was 5.5 months with maximum number of 18 (60%) patients below 6 months of age. There were 18 (60%) female and 12(40%) male patients with the F: M ratio of 3:2. Twenty six (87%) of the lesions were superficial and 4(13%) were deep. Twenty seven (90%) lesions were single and 3 (10%) were multiple. The site of the lesions was 22 (73.33%) on head & neck, 6 (20%) on trunk and 2 (6.66%) on limbs. In maximum number of 27 (90%) patients adequate response was obtained at 2mg/kg/day dose and only 3 (10%) cases required increased doses of 3mg/kg/day. The mean duration of treatment in the study was 7.8 months with a range of 6 months to 9 months. In maximum number of 22 (73.33%) patients there was good response with >50% reduction in the size of the lesions and 6 (20%) patients had excellent response with complete resolution of the lesions at the end of the study. Only 2 (6.66%) patients having large deep lesions had <25% reduction in size. All the 4 (100%) patients with ulcerated lesions showed complete resolution of ulceration and good response to therapy. Also colour changes were observed in almost all the patients from bright red colour at the beginning of treatment to light pink within 1-2 week's duration and then gradually lesion become pale or completely disappeared at the end of the study [*Fig1- 3*]. There were no major side effects of the drug observed except mild self limiting diarrhoea in 2 (6.66%) patients during the study period.

Discussion

Propranolol is a non-selective â- blocker that blocks the action of adrenaline on both â1 & â2 adrenergic receptors. Leaute-Labreze *et.al* (12) for the first time reported the effectiveness of propranolol in IHs. They presented a series of 11 children with severe IHs which improved even after the first day of treatment.

Since then, the drug has been used frequently for the management of IHs as first line therapy in various series reported in the literature (14). Oral Propranolol has three different pharmacological modes of action in IHs – early, intermediate & long term. The early effect is a visible change in colour and softening of the lesion seen within 1-3 days. This is due to â2 inhibitory effect that decreases the release of vasodilator transmitter like nitric oxide which causes vasoconstriction of the feeding capillaries (15). The intermediate effects are

Table.1 Showing various observations made during the study

S No	AGE(months)	SEX	LOCATION OF LESION	TYPE OF LESION	NO. OF LESIONS	INITIAL DIMENSIONS(Cm.)	FINAL DIMENSIONS (CM)	DURATION (MONTHS)
1	2	M	LEFT EAR	SUPERFICIAL	SINGLE	1 X 1	NIL	6
2	10	F	UPPER LIP	SUPERFICIAL	SINGLE	1 X 1	0.2 X 0.2	7
3	2.5	M	RIGHT EYELID,EAR	SUPERFICIAL	MULTIPLE	1 x 1	NIL	6
4	8	M	LEFT UPPER CHEST	DEEP	SINGLE	5 x 5	3 X 2	9
5	2.5	F	UPPER LIP	SUPERFICIAL	SINGLE	2 x 2	NIL	6
6	7	M	UPPER LIP	SUPERFICIAL	SINGLE	2 X 1	1 X 0.5	9
7	10	M	NAPE OF NECK	SUPERFICIAL	SINGLE	2 x 2	1 X 1	9
8	7	F	LEFT EAR	SUPERFICIAL	SINGLE	2 X 2	1 X 0.5	7
9	7	M	LOWER BACK	SUPERFICIAL	SINGLE	2 X 2	1 X 0.5	9
10	3.5	M	LUMBER REIGON	SUPERFICIAL	SINGLE	5 X 5	2 X 2	9
11	1.5	M	NAPE OF NECK	SUPERFICIAL	SINGLE	2 x 2	1 X 0.5	8
12	10	F	FOREHEAD	SUPERFICIAL	SINGLE	1 x 1	NIL	6
13	4	F	GLUTEAL REGION	SUPERFICIAL	MULTIPLE	6 X 6	3 X 2	9
14	10	M	ABDOMINAL WALL	DEEP	SINGLE	10X10	5 X 5	9
15	5	F	EAR	SUPERFICIAL	SINGLE	1 x 1	0.5 X 0.5	8
16	11	F	NECK	SUPERFICIAL	SINGLE	2 x 2	0.5 X 0.5	7
17	2	F	EAR	SUPERFICIAL	SINGLE	1 x 1	0.5 X 0.5	7
18	12	F	PERINEUM,RIGHT LEG	DEEP	MULTIPLE	6 x 6	3 X 2	9
19	3	F	CHIN	SUPERFICIAL	SINGLE	1 x 1	0.5 X 0.5	9
20	2.5	F	NOSE	SUPERFICIAL	SINGLE	1 x 1	NIL	6
21	5	M	NAPE OF NECK	SUPERFICIAL	SINGLE	0.5 X 0.5	0.25 X 0.25	6
22	2	M	LEFT LEG	SUPERFICIAL	SINGLE	4 x 4	4 X 3	9
23	3.5	F	NOSE	SUPERFICIAL	SINGLE	1 x 1	0.5 X 0.5	8
24	3	F	NECK	SUPERFICIAL	SINGLE	2 x 2	NIL	6
25	10	F	EAR	SUPERFICIAL	SINGLE	1 X 1	0.5 X 0.5	8
26	6	F	NECK	SUPERFICIAL	SINGLE	2 X 2	1 X 1	8
27	7	M	RIGHT UPPER CHEST	DEEP	SINGLE	4 x 4	3 X 4	9
28	2.5	F	EAR	SUPERFICIAL	SINGLE	1 x 1	0.5 X 0.25	9
29	4	F	UPPER LIP	SUPERFICIAL	SINGLE	2 x 2	1 X 1	9
30	3.5	F	FOREHEAD	SUPERFICIAL	SINGLE	1 x 1	0.5 X 0.5	9

due to down regulation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factors (b FGF). This inhibits proangiogenic cascade and decreases angiogenesis in the proliferative phase of growth of the lesion(16). The long term effect of the drug is due to apoptosis resulting in regression of the haemangioma(15,16). In our study most of the patients were given doses of 2mg/kg/day in two equal doses ex-

Fig. 1

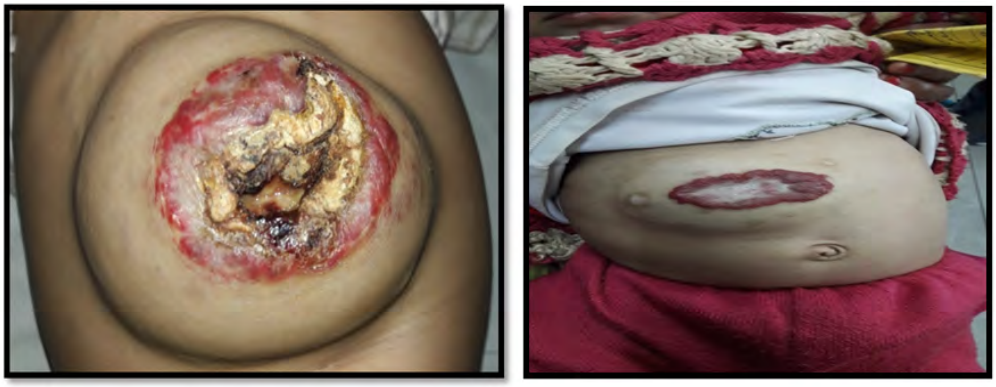


Fig.2

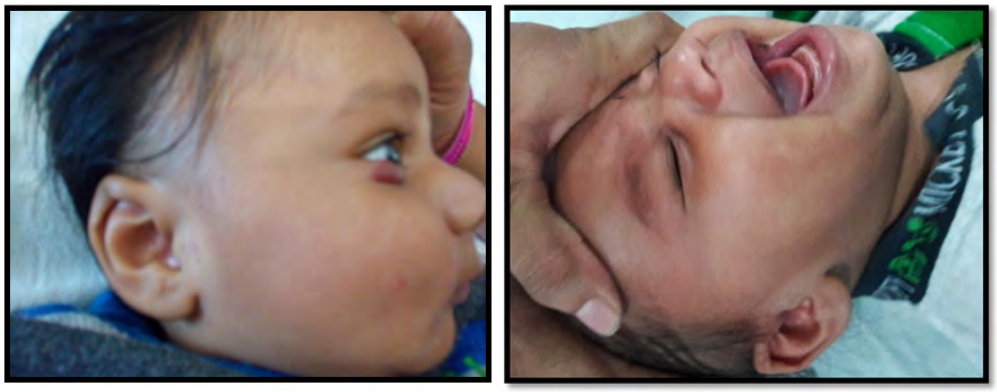
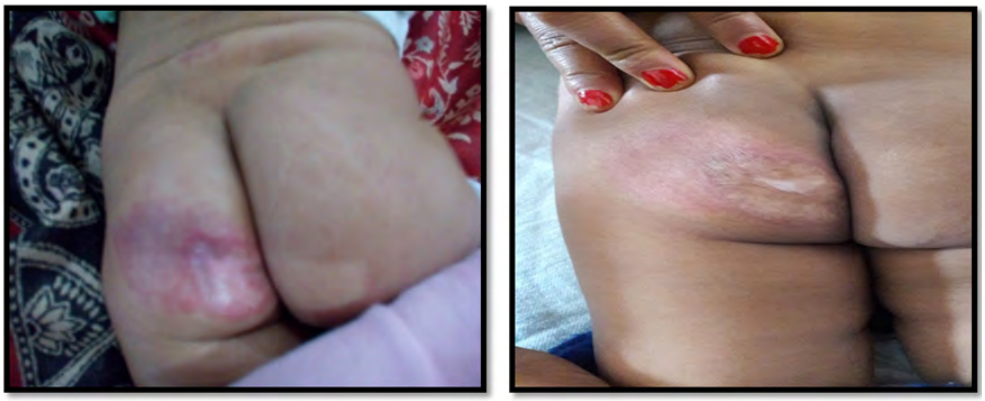


Fig.3



cept 3 patients with ulcerated & deep lesions where dose was increased to 3mg/kg/day. The mean duration of treatment was 7.8 months (range 6-9 months). McGee P *et.al*(17) have also used the same dosage over a mean period of 10.5 months in their study while Sergio L *et.al*(18) used a mean dosage of 2.8mg/kg/day (range 2.5-3.2 mg) for a mean duration of 12 months and El-Sabbagh AH. (19) has recently used a mean dosage of 3mg/kg/day over a period 3-4 months in their series. In the present series, all the patients responded well to the treatment with complete resolution of the lesions in 6 (20%) & >50% resolution in majority 22 (73.33%) similar to the series reported by Bagazgoitia L *et.al* (20) who found average reduction of 60% & El-Sabbagh *et.al*(19) who has found that all the 15 patients in their study responded well to the treatment and there was

50% reduction in the size of the original lesion. In our study, in all the lesions colour changes were also observed during the treatment from bright red to pink initially and then gradually pale. Similar colour changes have been observed in various other series (19, 20). All the 4 patients with ulcerated lesions responded well to the treatment leading to healing of ulceration similar to the other studies by Bagazgoitia L *et.al* (20) in which 8patients & Hermans DJ *et.al* (21) in which all the 20 patients having ulceration were cured. The potential side effects of the propranolol reported are bradycardia, hypotension, and hypoglycaemia and this drug is also contra indicated in asthma. In our study only two patients had mild self limiting diarrhoea which did not imply any dose reduction or discontinuation of therapy. EL- Sabbagh AH (19) has also reported diarrhoea in 3 of the 15 patients during the treatment in their study. In our experience propranolol was equally effective for the treatment of IHs in both the sexes irrespective of location of the lesions on skin even beyond the proliferative phase. But early institution of therapy is suggested, since response has been good where therapy was commenced at 1month of age. Superficial lesions, ulcerated lesions and those with accelerated growth are more likely to respond early and in a better way. We therefore conclude that Oral propranolol should be used as first line therapy in all patients with infantile cutaneous haemangiomas at a dose of 2mg/kg/day. In complicated, large size and deep lesions, dose should be increased to 3mg/kg/day for better response. Furthermore to institute proper dose and enhance patient compliance, oral liquid propranolol preparations should be made available commercially in the market.

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