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Progress in the treatment of infantile hemangioma

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***Abstract*---**Infantile hemangioma (IH) is a common benign tumor, which mostly resolves spontaneously; however, children with high-risk IH need treatment. To compare the efficacy of single drug pharmacotherapy and combined drugs pharmacotherapy for a spectrum of Infantile Cutaneous Hemangiomas ranging from smaller and simpler lesions to large and complicated lesions selectively chosen. It is a Retrospective and Prospective study done for 2yrs. All children less than 2 years of age, with Infantile Cutaneous Hemangiomas. Infantile Cutaneous Hemangiomas not amenable for complete primary excision because of size and site of lesion are included in the study. Children with Infantile Cutaneous Hemangiomas presenting after 2 years of age and Hemangiomas associated with Visceral Hemangiomas. Infantile hemangiomas (IHs) are the most-common soft-tissue tumors of infancy, occurring in 4% to 10% of children under 1 year of age, with a clear female to male predominance of 2.5 – 4:1¬. 27(64.2%) presented with lesion in the head and neck region. Three (3) out of the 42 presented (7.1%) on the chest. Four (4) out of the 42 (9.5%) presented on the Anterior abdominal wall. Out of the 42 patients included in our study, 38 patients were given Propranolol only. Four (4) patients were given a

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combination of Propranolol and Prednisolone. While at initial follow-up of 1 month, size reduction was noticed in 35 (83%) patients(VAS Score -3 -> -5), by the second follow-up 38 cases showed a clinical response while 4 apart from the above 38 showed complete regression, hence 41 cases out of the 42 showed response to drug therapy by the 2nd follow-up. treatment was completed in 14 cases out of the 42. Twelve (12) cases showed complete resolution. One (1) case had a residual lesion and 1 case had residual telangiectasia. All the other 12 cases showed complete resolution of the lesion with no recurrence. In conclusion, our study showed that propranolol therapy was more effective in lesion clearance, and demonstrated superior tolerance, with negligible adverse effects.

***Keywords*---**infantile hemangiomas, propranolol, prednisolone.

Introduction

Infantile hemangiomas (IHs) are the most-common soft-tissue tumors of infancy, occurring in 4% to 10% of children under 1 year of age, with a clear female to male predominance of 2.5 – 4:1. Multiple lesions are found in 15–30% of patients with infantile hemangiomas. Recognized risk factors for the development of hemangiomas include prematurity, fair skin and female sex, with ratios ranging from 1.4:1 to 3:1. Infantile hemangiomas affect whites more commonly than they do Hispanics or African Americans. Compared with the general population, mothers of patients with IHs are of higher maternal age, have a higher incidence of pre-eclampsia or placenta previa and are more likely to have multiple gestation pregnancies. [1,2]

Infantile hemangiomas usually are superficial involving the skin and therefore obvious on physical examination, but they can also be deep (subcutaneous) with or without skin changes. IHs can be focal, segmental or indeterminate. Focal hemangiomas are more common and present as localized, raised and tumor-like lesions. Segmental hemangiomas are flat, larger, plaque-like and geographical in a segmental distribution. Indeterminate lesions do not entirely encompass an accepted embryological segment or arise from a single focus and can demonstrate mixed features. On occasion, IHs are completely confined to the subcutaneous soft tissues, presenting as a bluish lump with intact overlying skin.[3]

At birth, IHs may not be apparent or may appear as flat circumscribed lesions with telangiectatic vessels on the surface. Approximately 30% have a precursor lesion indicated by the presence of a macule, an area of discoloration or telangiectasia Within the first weeks of life, IHs enter a phase of rapid growth with superficial and/or deep components, which lasts usually 3 to 6 months and sometimes up to 24 months. A period of stabilization for a few months follows, and spontaneous involution usually occurs in several years. Regression is complete for 60% of 4-year-old patients and 76% of 7-year-old patients. Most of the times, sequelae are minimal, with residual cutaneous redundancy, fibrous and fatty residues, and telangiectases, which can be treated with late surgery or pulsed-dye laser therapy. Because of this benign, self-limited course, therapeutic

abstention is the rule.

However, 10% of IHs require treatment during the proliferative phase, because of life-threatening locations, local complications, or cosmetic/functional risks. IHs can be life-threatening when present in upper airways and liver, inducing acute respiratory failure and congestive heart failure, respectively. In addition, IHs cause at least transient cosmetic disfigurement, which may trigger psychological morbidity first in parents and later in affected children. Hemangiomas in certain anatomic regions are especially likely to cause psychosocial problems, such as those in the nasal tip, glabella, and cheek.

The conventional approach in complicated cases is to use systemic corticosteroid therapy as first-line treatment and then interferon or vincristine as second- or third-line therapeutic agents. Even with high dosages (2–5 mg/kg per day), rates of responses to systemic corticosteroid therapy (stabilization or incomplete regression, in most cases) range from 30% to 60%, with the effects appearing within the first 2 or 3 weeks of treatment. [4] Moreover, side effects are multiple; most are transient and limited, such as cushingoid facies, insomnia, irritability, stunted growth, and gastrointestinal symptoms, but some may become much more serious, such as hypertension and hypertrophic obstructive cardiomyopathy. Intralesional corticosteroids used for treating palpebral hemangioma can lead to central artery occlusion. Complete response to interferon (either 2a or 2b) at 1-3 U/m^2/ day has been seen in 40- 50% of complicated cases with the first signs of regression appearing 2-12 weeks of treatment. Frequent side effects include fever and muscular pains at the beginning of treatment. Hematologic and hepatic toxicity, hypothyroidism, and neurotoxicity with spastic diplegia and development delay may occur. Another recent treatment option is vincristine given at 0.05 mg/kg or 1 mg/m2 infusions once a week. Efficacy is close to 100%, with IH involution beginning 3 weeks after treatment. Significant side effects include constipation, transient jaw pains, peripheral neuropathy, hematologic toxicity, and inappropriate secretion of antidiuretic hormone.[5]

However, oral prednisolone therapy remains one of the most common treatment modalities for proliferating hemangiomas and has been the drug of choice for outpatient therapy in our department. Steroids have been shown to be antiangiogenic in a number of in vitro settings. Additionally, steroids may influence capillary vascular tone. While their efficacy is not disputed, children are liable to complications, like gastritis, Cushing's syndrome, and growth retardation.[6] Propranolol, a well-tolerated, nonselective, ß-adrenergic receptor blocker has been commonly used so far for cardiologic indications in young children. In 2008, Léauté-Labréze et al. reported the incidental finding that propranolol can control the growth of IHs efficiently. Other studies done since then on this drug have shown an excellent effect and good tolerance. Within hours of starting therapy, propranolol produces vasoconstriction, resulting in a reduction in the color of the hemangioma. Its primary effect, however, appears to be alteration in the progression of angiogenesis in the hemangioma. Regulation of hemangioma growth involves basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Léauté-Labréze and colleagues theorized that propranolol may decrease expression of bFGF and VEGF. Based on examination of hemangioma tissue, Truong and coworkers have also speculated that beta-

adrenergic antagonists may ablate catecholamine receptor signaling, decreasing cyclic AMP and reducing levels of VEGF. In addition, propranolol may promote involution of hemangiomas by triggering apoptosis in endothelial cells.[7,8] There is no strict evidence- based studies to guide the therapy. Moreover data regarding comparative efficacy of steroid and propranolol is inadequate and overall number of children studied, given the high incidence of hemangioma is also inadequate.

Materials and Methods

It is a Retrospective and Prospective study done for 2yrs during January 2014 to December, 2017**.** In the Department of Pediatric Surgery, Niloufer Institute of Women and Child Health, Hyderabad, Telangana. All children less than 2 years of age, with Infantile Cutaneous Hemangiomas, presenting to Pediatric Surgery outpatient Department in Niloufer hospital are included in the study. Infantile Cutaneous Hemangiomas not amenable for complete primary excision because of size and site of lesion are included in the study. Children with Infantile Cutaneous Hemangiomas presenting after 2 years of age and Hemangiomas associated with Visceral Hemangiomas are excluded in the study. Forty two (42) patients with cutaneous infantile hemangioma were included in this study out of which 30 (71.4%) were female and 12 (28.6%) were male. The age of the patients ranged from 12 days to 18 months. The majority of patients, 66.6% were less than 6 months of age.

At our study each lesion was evaluated clinically for size, colour, and consistency. The maximum diameter in 2 axis perpendicular to each other would be measured. The lesion was photographed with and without flash with a 12-pixel camera. Electrocardiographic evaluation was done to rule out treatment contraindications. GRBS was done 4 hours after initiation of treatment. USG abdomen and NSG was done to rule out visceral and intracranial hemangiomas. Patients were started on propranolol at an initial dose of 1mg/kg/ in 2 divided doses. The patients attendants were also asked to increase the frequency of feeds after giving the medications. Clinical assessment with measurements and photographs was repeated after 1 month of starting treatment. After the first follow up, the dose of propranolol was increased to 2mg/kg in 2 divided doses. Patients with large lesions involving the head and neck were started on a combination of propranolol and prednisolone in the hope of quicker response. Prednisolone was initiated at a dose of 2mg/kg in 3 divided doses. Syrup Sucralfate was also added to patients to whom prednisone was given. Previous records of the patients were reviewed and a detailed history was obtained and physical examination was done.

All the children were reevaluated after 30 days of treatment and then at 3months followed by 6 months and further depending on the response. Doses were adjusted according to weight on follow-up. Follow-up evaluation consisted of clinical and photographic assessment of the IH and monitoring of treatment compliance and tolerance (heart rate and blood pressure). Although not a part of the study, treatment was continued till the age of 1 and a half years unless complete resolution occurred earlier. Therapy was tapered off over the last month and patients were continued on follow-up to look for relapse. Measure of assessment was based on Visual Analogue Scale ranging from −10 to +10 by comparing follow-up images to the baseline photograph pre treatment. On the

visual analogue scale 0 represented the baseline photograph (pre-treatment), a decrease in colour or size resulting in a -(negative) number and an increase in colour or size in a +(positive) number.

Results

The total number of patients with IH was 42. All these patients underwent evaluation with complete blood picture, GRBS, USG abdomen and Neurosonogram. The management of Infantile Hemangioma was as per standard protocol.

Table1
Demographic details in study

Gender	Number of patients	percentages
Females	30	71.4
Males	12	28.6
Total	42	100
Age distribution		0
0-6 months	28	66.7
7-12 months	11	26.2
13-18 months	3	7.2
Site of lesion		0
head and neck region	27	64.5
Chest	3	7.2
Anterior abdominal wall	4	9.5
upper limbs	3	7.2
Lower limbs	3	7.2
Labia majora	2	4.8

Out of the 42 patients, 30(71.4%) were female and 12(28.6%) were male. The age of the patients ranged from 12 days to 18 months with a mean age of presentation of 5.7 months. Out of 42 patients, 27(64.2%) presented with lesion in the head and neck region, 3(7.1%) on the chest, 4(9.5%) presented on the Anterior abdominal wall, 3(7.1%) in the upper limbs and 3(7.1%) on the lower limbs, 2(4.7%) presented on the labia majora. Thirty-eight patients were given Propranolol only. Four patients were given a combination of Propranolol and Prednisolone. Patients given prednisolone were also given sucralfate. Three patients were given a combination of Propranolol and antibiotic as they presented initially with an ulcer. The antibiotic used was Amoxicilian/Clavulanic acid (dose-50mg/kg/dose) and was stopped after giving for 5 days. The initial dose of propranolol was 1mg/kg in 2 divided doses. The dose was then increased to 2mg/kg in 2 divided doses after a month. All the patients' attendants were asked to increase the frequency of feeds to whom propranolol was given. Prednisolone was given at a dose of 2mg/kg in 3 divided doses.

Drug response

Out of the total 42 patients included in the study, 41 cases showed response to drug therapy (97.61%). Complete resolution was noted in 12 patients. One case has residual lesion but no recurrence was noted after stopping treatment. one case had residual telangiectasia. Treatment was stopped in all these 14 cases and rest of the 27 cases are still on follow-up. Two out of the 14 cases for whom treatment has been stopped are under follow up for recurrence. In the rest 12 cases no recurrence has been observed. The results have been divided under 4 categories with respect to: 1) Size, 2) Flattening 3) Consistency and 4) Colour

Size

At initial followup of 1 month, size reduction was noticed in 35 patients (VAS Score -3 -> -5). Three patients did not show reduction in size in the first follow-up whereas in 4 patients a mild reduction was noticed, (VAS score 0 -> -2).

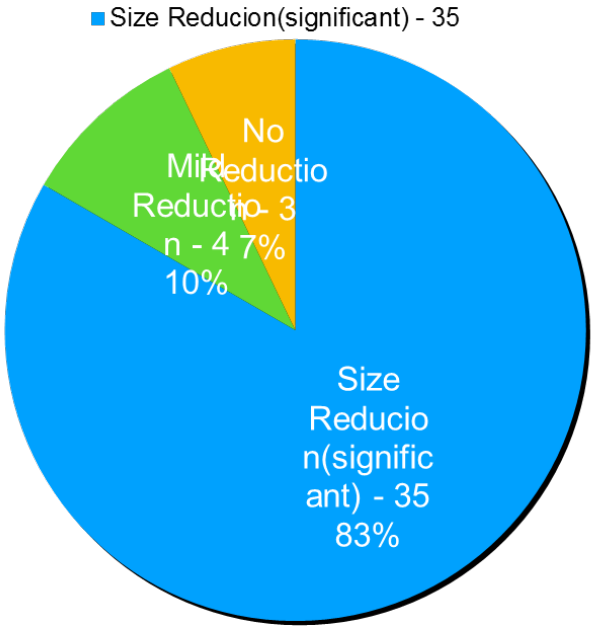

Figure 1. Size reduction after the commencement of starting the treatment

The second follow-up was done at 3 months after the commencement of starting the treatment. Three cases (n=3) showed complete regression out of the 42. One case showed no response to propranolol and 38 cases showed significant improvement with respect to size on the VAS score (-4 -> -5). All the above cases were given propranolol only. Ten (n=10) patients were followed up beyond 6 months in our study. One patient did not respond to any medical therapy. Eventually all medical management was stopped for that patient. Four out of the remaining 9 showed complete regression of the lesion by 6 months of age. The medications were stopped in these 3 of them and no recurrence was observed. Out of the 3, 1 patient was given a combination of steroids plus propranolol.

Rest were given only propranolol. One patient is still under observation and continues to show good response. Five patients (n-5) were followed up beyond 1 year of starting treatment. One patient showed regression (VAS score -5) and treatment was stopped. no signs of recurrent growth were noted. In 2 patients medication was continued for 18m after which and was stopped after it showed no residual hemangioma. 2 pati ents showed regression after 1 year of starting treatment. Treatment was stopped and no signs of recurrence was noted.

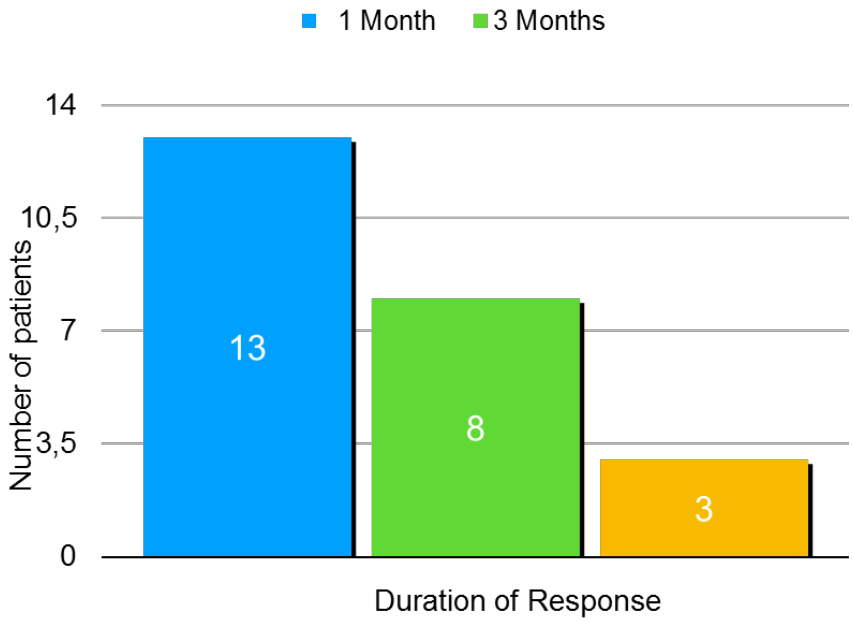

Figure 2. Regression according to duration

Flattening of Lesion

In case of elevated IH, the drug response was also noted with respect to flattening of the lesion. This aspect was documented on all follow-up according to the VAS score. Out of the 42 cases, flattening could not be evaluated in 10 cases due to the location and type of presentation of the lesion. These were the lesions presenting with subcutaneous extension. Thirty-two cases presented with predominant cutaneous lesion in which the elevation of the lesion could be assessed. Out of these 32 patients, 13 showed flattening in the 1st follow-up after 1 month of initiation of treatment, 8 showed flattening after 2nd follow up of 6 months, 3 cases showed flattening after 6 months. Eight cases did not show flattening till the 2nd follow-up (6months). These are still being assessed.

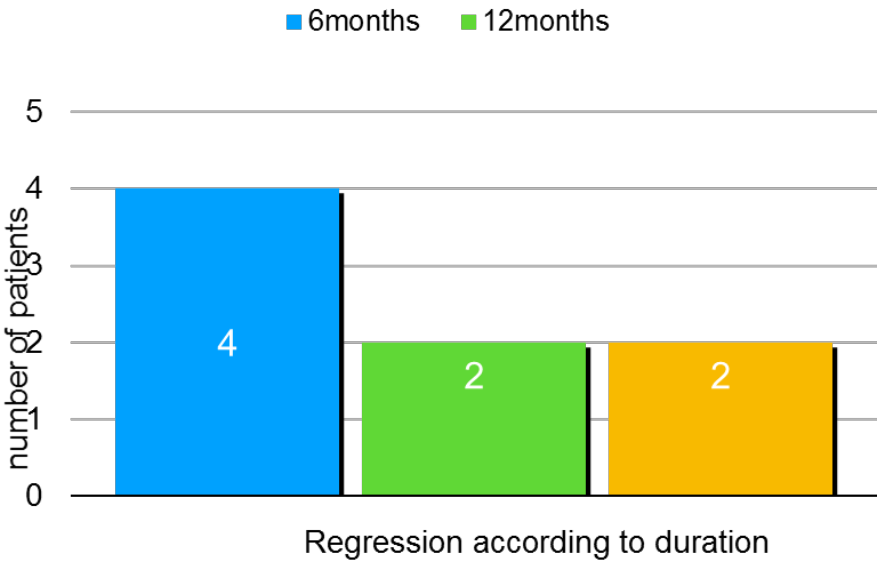

Figure 3. Duration of response in study

Consistency

Twenty-four cases out of the 42 patients initially presented with firm consistency lesion. Out of the 24 cases, 20 cases showed softening of lesion after the 1st month of initiation of treatment. 4 cases showed softening in consistency after the 2nd follow-up of 3 months. The lesions remained soft throughout the period of treatment.

Colour

Out of the 42 patients, colour could not be assessed in 8 patients due to their sub cutaneous extension. In the remaining 35 patients, 19 showed fading of colour in the 1st month follow-up, 15 showed fading of colour by 3months and 1 showed fading in the 3rd follow-up by the 6 month.

Ulceration

Three cases in our study presented with ulceration. These cases were given propranolol and antibiotic only. The ulcer disappeared by 1 week of antibiotic therapy in all the 3 cases.

Cases with complete resolution

Out of the 42 cases in our study, treatment was stopped in 14 cases, 12 showed complete resolution, 1 case had a residual lesion and 1 case had residual telangiectasia. All the other 12 cases showed complete resolution of the lesion with no recurrence. The mean duration of treatment in these cases was 7.5 months. The mean age at presentation was 4.3 months. Out of these cases, 10 were located in the head and neck region, 1 in the anterior abdominal wall. 2 on

the chest and 1 in the lower limb.

Discussion

Infantile hemangiomas (IHs) are the most-common soft-tissue tumors of infancy, occurring in 4% to 10% of children under 1 year of age, with a clear female to male predominance of 2.5 – 4:1.[1] In our study, we noted a female preponderance, being 30 against 12 males with a ratio of 2.5 : 1. A rapid growth phase usually begins in the first few weeks of life and continues until 9 to 12 months of age. In our study, all patients noticed the lesion in the first few weeks of life but presented to us later. Even then, the majority of the patients (n=30) presented before the age of 6 months. Eleven (n=11) patients presented to us between the age of 7-12 months. These patients too gave a history of the lesion being seen few weeks after birth. Three (n=3) patients presented to us after the age of 12 months with the oldest child being 18months. On history taking, all the above patients attendants gave a history of gradual growth of the lesion. On enquiring regarding the delayed presentation, they all gave the same history of the treating pediatrician asking them to wait and observe for spontaneous resolution.

In our study we have found that Out of the 42 patients, 27(64.2%) presented with lesion in the head and neck region. This shows that majority of the lesions occur in the head and neck region. Three (3) out of the 42 presented (7.1%) on the chest. Four (4) out of the 42 (9.5%) presented on the Anterior abdominal wall. Three (3) out of the 42 presented(7.1%)in the upper limbs and an equal number of patients presented in the lower limbs also. Two (2) out of the 42 (4.7%) presented on the labia majora in our study. With respect to age, majority patients with head and neck lesions presented to us before the age of 6 months.(20 out of the 27). The rest presented later and on history, hope for spontaneous reduction was the explanation given by the parents for the delay in seeking treatment. Majority of the head and neck lesion patients presented before due to cosmetic reason. Even the ones who presented later often did as they were scared regarding the cosmetic aspect and wanted to seek intervention.

Table 2
Studies in comparision in variables

Studies	Mean age at presentation(months)
Léauté-Labréze et al[7]	3.2
Sans et al[9]	4.2
Manunza et al[10]	5.8
Our study	5.7
Steroid	
Rössler J, Wehl G and Niemeyer C.M (oral steriods)[11]	85%
Bennet et al (oral steroids)[4]	84%
Kushner (intralesional steroids)[12]	84%
Our study	97.6%
Dosage (mg/kg)	
Léauté-Labréze et al[7]	2

Sans et al[9]	2-3
Manunza et al[10]	Started at 1 followed by 2
Buckmiller et al[13]	2
Bagazgoitia L and Torrelo A [14]	2
Schill T, Maruani A et al[15]	2
Our study	Started at 1 followed by 2

In our study, the mean onset of age of presentation is 5.7 months. Léauté-Labréze et al [7]in 2008 first described use of propranolol with an average age at the onset of therapy was 3.2 months (range 2-6 months). Sans et al. gave Propranolol was given to 32 children with a mean age a onset of treatment was 4.2 months. Manunza and colleagues[10] briefly described their experience with propranolol in 30 His with the average patient age at the start of therapy was 5.8 months which was almost same as our study. Out of the 42 patients included in our study, 38 patients were given Propranolol only. Four (4) patients were given a combination of Propranolol and Prednisolone. Patients given prednisolone were also given sucralfate. 3 patients were given a combination of Propranolol and antibiotic as they presented initially with an infected ulcer. The antibiotic used was Amoxicillin/Clavulanic acid (dose- 50mg/kg/dose) and was stopped after giving for 5 days.

Prednisolone and propranolol were given initially in 4 patients who presented with extensive lesion on the head and neck region involving the eyelid and the lip. One (1) patient did not respond to any form of treatment which included single drug and multiple drug therapy. The same patient complained of irritability and insomnia when placed on steroid therapy. One (1) patient on combination therapy of propranolol and steroid presented to us with an injection abscess on the second follow-up which was drained. The child was tapered off prednisolone and was continued only on propranolol and the lesion had completely resolved by the 6th month. Boon et al evaluated 62 patients receiving systemic steroid therapy for problematic IH, the following complications were seen: cushingoid facies 44 (71%), personality changes 18(21%), gastric irritation 13(21%), fungal infection 4(6%) and reversible myopathy (one patient).[22] We in our study found two of the complications as observed in the above study though the number is inadequate for a statistical reference.

As the study was being conducted in a peripheral center with patients coming from distant places with scarce mode of transport and telephonic facilities, we chose to withhold the use of prednisolone. The other patients were subsequently followed up for the response on propranolol only. When we compare our study to the studies conducted for response to steroids only, our study showed better response with propranolol when compared to steroid only. While Rössler J, Wehl G and Niemeyer C.M[11] reported an efficacy of 86%, Bennet et al[4] reported an efficacy of 84%. Kushner et al [12] reported the use of intralesional steroids in IH with an efficacy of 84%. In comparison to this, we reported a higher efficacy with Propranolol with 97.6% in our study. Response to propranolol has been promising in our current study. While at initial follow-up of 1 month, size reduction was noticed in 35 (83%) patients(VAS Score -3 -> -5), by the second follow-up 38 cases showed a clinical response while 4 apart from the above 38 showed complete regression, hence 41 cases out of the 42 showed response to drug

therapy by the 2nd follow-up.

Léauté-Labréze et al[7] in 2008 for the first time in the literature reported the benefit of propranolol in the treatment of severe IHs. The first patient was treated with an oral propranolol dose of 3 mg/kg/day, while the remaining patients received 2 mg/kg/day, which was same as our study. All patients demonstrated improvement in the size and colour of their hemangiomas. Which was same as in our study. Sans et al.[9] reported the efficacy of propranolol to be 100% in 32 patients with good clinical tolerance. Propranolol was administered to 32 children with a starting dose of 2 to 3 mg/kg per day, given in 2 or 3 divided doses. Immediate effects on color and growth were noted in all cases. In comparison to our study, the results are almost similar with significant response as per VAS score. In ulcerated IHs, complete healing occurred in 2 months in Sans et al and in comparison, to our study showed healing of ulceration by the 1st month. Sans et all administered treatment for a mean total duration of 6.1 months which was less than our study which stands at 8.5 months. Relapses were mild and responded to retreatment as seen by Sans et all where as in our study we did not encounter any relapses. One patient was reported to have discontinued treatment because of wheezing but this complication was not noted in our patients.

Manunza and colleagues[10] briefly described their experience with propranolol in 30 IHs.[34] Nine (9) of the patients were treated after failure to respond to corticosteroids. Two were treated with both prednisolone and propranolol, while the rest received only Propranolol. In comparison, in our present study 4 out of 42 were treated with both. Oral propranolol solution was initiated at a dose of 1 mg/kg/day (divided into three daily doses) and If tolerated, the dose was increased to 2 mg/kg/day after 1 week by Manunza et al.[10] In this study, the dose was increased after a month if tolerated. Treatment continued for 1 year unless complete resolution occurred earlier, and therapy was tapered off over the last month. Nineteen (19) infants had successfully completed treatment and the remaining patients had demonstrated significant improvement. In our study, 14 patients completed treatment and no significant adverse effects were reported as was by Manunza et al.[10]

Buckmiller et al[13] ; Bagazgoitia L and Torrelo A[16] ; Naouri M, Schill T, Maruani A et al[10] all started treatment with a dose of 2mg/kg/day. In our study, we start with a dose of 1mg/kg/day and then increase to 2mg/kg/day by the 1st follow-up. The results in our study did not show any difference when compared with the studies of the above-mentioned authors. Bonifazi[38] started treatment with 2mg/kg/day which was divided in 3-4 dose. In comparison, in our study we gave the same dose in 2 divided doses. All the patients tolerated the medication with no adverse effects, hence concluding that frequency may not be a major factor for response.

Kima L.H.C, Hogeling M, Wargon O et al[17] presented 6 cases of ulcerated IH, which responded to oral propranolol within 2 to 6 weeks and recommended that oral propranolol therapy be considered for the management of ulcerated IH as first line of treatment. In our study, 5 cases presented with ulceration out of which 3 were infected. We started on the same dose but also included an antibiotic for 1 week in view of the infection associated with the ulcer. All the

ulcers healed by 4 weeks in our study which is similar to the above-mentioned study.

Cynthia J.P, Carol L and Bertha B et al[18] in a study conducted at the University of Miami and Miami Children's Hospital, compared the use of propranolol with corticosteroids in 110 patients with infantile hemangiomas They found that 82% of patients in the propranolol group improved by 75% or more, compared with 29% of patients in the steroid group. One patient on propranolol had hypoglycemia, but all patients in the steroid group had at least one adverse event. In our study though we did not compare the results directly between propranolol and steroids, but the complications were higher in steroid group. We did not face any complications with propranolol either. In conclusion, the researchers also found propranolol therapy was more cost-effective when compared to steroids, with a total cost reduction of more than 50% per patient.

Table 3
Comparision of our study in response after completed treatment

Study groups	Response	Completed treatment
Léauté-Labréze et al (n=11)[7]	11	7
Sans et al (n=32)[9]	32	NA
Manunza et al (n=30)[10]	30	19
Buckmiller et al (n=32)[13]	32	NA
Our study(n=42)	41	14

In the present study, treatment was completed in 14 cases out of the 42. Twelve (12) cases showed complete resolution. One (1) case had a residual lesion and 1 case had residual telangiectasia. Lister in 1938 first described the natural history of growth and regression of infantile hemangioma.[19] with mild residual changes include telangiectasias, atrophic wrinkling, or yellowish discoloration. Telangiectasia was noted in 1 of our cases as described by Lister. Scarring was also described by Lister especially if ulceration occurred which was noted in all the 5 cases which presented to us with an ulcer in our study. All the other 12 cases showed complete resolution of the lesion with no recurrence. Patients were monitored for a period of 3 months after stopping the medication to check for recurrence. None of the cases showed any signs of relapse. The mean duration of treatment in these 14 cases was 8.5 months. The shortest duration being 2months and the longest being 18 months.

Out of the 14 cases in which treatment was completed, 11 of them presented to us on/before the age of 6 months. Remaining 3 presented after 6 months of age. The lesions which presented to us before 6 months of age provided a better result than the one who presented at a later date. The primary effect of propranolol appears to be alteration in the progression of angiogenesis in the hemangioma. Regulation of hemangioma growth involves basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Léauté-Labréze and colleagues theorized that propranolol may decrease expression of bFGF and VEGF. Based on examination of hemangioma tissue, Truong and coworkers have also speculated that beta-adrenergic antagonists may ablate catecholamine receptor signaling,

decreasing cyclic AMP and reducing levels of VEGF. In addition, propranolol may promote involution of hemangiomas by triggering apoptosis in endothelial cells. Storch et al.[21] recently summarized the current knowledge on the molecular mechanisms involved and attributed the striking effect of propranolol on growing IHs to vasoconstriction, inhibition of angiogenesis, and induction of apoptosis. These correspond to early (brightening of hemangioma surface), intermediate (growth arrest), and long-term (regression) clinical observations. Hence with these observations, we can infer that the earlier the treatment is started, the better results can be achieved.

Out of the 14 cases which reported complete regression in our study, 9 were located in the head and neck region, 2 in the anterior abdominal wall, 2 on the chest and 1 in the lower limb. With this data we can infer that head and neck lesions show early signs of regression when compared to lesions on other body parts. A meta-analysis done by Chinnadurai S, Fonnesbeck C, Snyder KM, et al [21] which included 18 studies in a network meta-analysis assessing relative expected rates of IH clearance associated with □-blockers and steroids from a period of 1982-2015 concluded that oral propranolol had the largest mean estimate of expected clearance (95%; 95% Bayesian credible interval [BCI]: 88%–99%) relative to oral corticosteroids (43%, 95% BCI: 21%–66%) and control (6%, 95% BCI: 1%–11%). Strength of evidence (SOE) was high for propranolol's effects on reducing lesion size compared with observation/placebo. Corticosteroids demonstrated moderate effectiveness at reducing size/volume (moderate SOE for improvement in IH).

Conclusion

Treating IHs with oral propranolol hydrochloride until the end of the proliferative phase appears to be very effective, and the evidence supports its use as a first-line option for potentially disfiguring or complicated IHs. Due to the heterogeneous nature of IHs, duration of treatment with propranolol will likely need to be individualized depending on the child's type of IH and response to treatment. In conclusion, our study showed that propranolol therapy was more effective in lesion clearance, and demonstrated superior tolerance, with negligible adverse effects. Propranolol proved to be safe in treating IH in our patients as no major adverse effects occurred. The earlier the treatment started, better the results that can be achieved with propranolol. Therefore, based on the results of our study, we believe that propranolol therapy is superior to traditional first-line oral corticosteroids in the treatment of IH and propranolol be considered a first-line agent given its safety and efficacy for the treatment of IH.

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