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ORIGINAL RESEARCH

Comparison of oral Propranolol with topical Timolol in the treatment of Superficial Infantile Hemangiomas

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Abstract

Background: Infantile Hemangiomas (IHs) are common, benign and self-limiting vascular malformations. A significant percent of these vascular lesions are associated with substantial morbidity and cosmetic disfigurement, therefore treatment should be initiated as soon the diagnosis is confirmed especially for the hemangiomas involving vital areas [1]. Oral propranolol has now been a time tested drug for the successful management of superficial IHs; but factors like risk of hypoglycemia, contraindication among babies suffering from allergic respiratory conditions and non-compliance in disfavor its usage in certain children [2]. Topical timolol suits well in these patients as the action is mainly localized at the site of its application. The present study was designed to compare efficacy of these two drug modalities in the treatment of superficial infantile hemangiomas.

Patients and methods: This randomized controlled study included 20 children in two groups receiving either oral propranolol or topical timolol. Clinical parameters in the form of systolic and diastolic blood pressure (SBP & DBP), heart rate (HR), respiratory rate (RR), random blood sugar (RBS), oxygen saturation (SaO_2), haemangioma activity score (HAS) & physician global assessment scale (PGA) were recorded and compared well in both the groups till eighteen months.

Results: The groups were statistically comparable with respect to the age, sex, gestational age, birth weight and severity of the vascular lesion. Head and neck regions were most commonly involved sites. Both propranolol and timolol were found to be safe and comparable with regard to the changes in HR, respiration pattern and blood sugar levels. However, slightly low DBP was observed in the propranolol group at 20^{th} week when compared with timolol group (p value- 0.007). On clinical analysis, fall in HAS was significantly lower in propranolol treated babies from 20^{th} week onwards. The gain in the PGA score was more in propranolol patients and the difference was statistically significant particularly at 18 months (p value- 0.04).

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Conclusion: We conclude that both the treatment modalities can be administered safely. However, oral propranolol offers better results than topical timolol in terms of clinical response as a whole.
Keywords: Superficial infantile hemangioma, Beta blockers, Propranolol, Timolol, Vascular lesions.

Introduction

Infantile haemangiomas (IHs) are the most common soft-tissue tumours of infancy, occurring in about 4-10% of all infants [2]. The cause of haemangioma is still unknown, but it is closely associated with the disorder of angiogenesis and vasculogenesis [3]. A rapid growth phase usually begins in the first few weeks of life and continues till 9-12 months of age. Subsequently, the majority of the haemangiomas undergo a spontaneous slow but extensive involution [2]. These lesions are generally noted within the first two weeks of postnatal life. However, there is wide variability in this timing. Overall, 80% of cutaneous haemangiomas are single, whereas 20% of them are multiple. Haemangiomas occur most commonly in the craniofacial region (60%), followed by the trunk (25%) and extremities (15%). These lesions are three to five times more common in females with an even higher female preponderance in haemangiomas that are problematic or associated with structural abnormalities [4].

IH risk factors include white race, prematurity, low birth weight, advanced maternal age, multiple gestation pregnancy, placenta praevia and pre-eclampsia. Other risk factors may include in utero diagnostic procedures (chorionic villus sampling and amniocentesis), use of fertility drugs or erythropoietin, breech presentation, and being first born [5]. Although many haemangiomas are benign and innocuous, a significant subset is life altering (causing permanent visual loss, disfigurement, and pain from ulceration) and a smaller subset is life threatening [1].

There are virtually no rigorous evidence-based studies to guide therapy. Moreover, there are no FDA-approved medical treatment options for haemangiomas. Glucocorticoids have been the mainstay of therapy from 1960s but their mechanism of action is not well understood and they have many potential side effects making the therapy more complicated. Intra-lesional steroids can lead to corticosteroid particle embolization, ophthalmic artery occlusion, retinal embolization and central retinal artery occlusion, linear subcutaneous fat atrophy, eyelid necrosis and periocular calcification [6]. Resection of a proliferating IH generally is not recommended because younger patients are at greater risk of anaesthetic morbidity, blood loss, and iatrogenic injury than those who undergo operative intervention later in childhood [7].

In 2008, a report of serendipitous improvement of IH in infants treated with beta blocker therapy (propranolol) opened the gateway for trial of newer options for the medical therapy of IHs [6, 8]. Beta blockers, either applied topically or used systemically constitute a new and promising treatment modality. Various explanations have been proposed including vasoconstriction, decreased expression of vascular endothelial growth factor and beta fibroblast growth factor genes, apoptosis of capillary endothelial cells, blockage of the G protein-coupled receptor kinases Leu41, reduced matrix metalloproteinase-9 and effect on differentiation of mesenchymal stem cells [1,9]. Numerous reports have suggested that oral propranolol holds high promise for infantile haemangioma treatment and other reports have focused on the effect of topical beta blockers with promising results [10]. Topical beta blockers like timolol have also been shown to be effective for cutaneous capillary haemangiomas. The major advantages of topical timolol are their availability, cost, ease of

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administration, and minimal risk of drug-related adverse events, especially when applied to the face and in particular the periorbital area [11].

To minimize potential side effects caused by systemic use of propranolol, recently topical application of beta blockers in the form Timolol has been studied extensively in the treatment of IHs. However, it is still controversial whether topical timolol is superior to oral propranolol in the treatment of superficial IHs. Hence, we aimed to conduct this study to evaluate the clinical efficacy and adverse effects of oral propranolol in comparison with topical timolol for the treatment of superficial infantile haemangiomas.

Material and methods

This was a randomized controlled study conducted over a period of 18 months where-in patients were divided into two well matched groups; group A received oral propranolol and group B was treated by topical timolol. This study was registered with Clinical Trials Registry of India with reference no. CTRI/2021/05/033307. Group A received propranolol with a starting dose of 0.5mg/kg/day (as crushed tablets) in two divided doses and the dose was escalated to 1-1.5 mg/kg/day after 24 hours if tolerated well. Group B received topical timolol given at a starting dose of 0.25% hydrogel once daily dosage and increased to 0.50% hydrogel after 24 hours if tolerated well. During each follow up, which were done at 4 week, 8 week, 12 week, 16 week, 20 week, 24 week, 28 week, 32 week, 36 week and 18 month; weight, SBP, DBP, HR, RR, RBS, SaO_2, HAS and PGA score were recorded [12]. HAS and PGA score were calculated by an independent surgeon blinded to the management protocol with the help of photographs at monthly intervals.

Unpaired t-test was used to compare means for quantitative variables like age, gestation age, weight, SaO_2, SBP, DBP, RBS, RR, HAS and PGA. Chi-squared tests or Fisher's exact tests was used to compare the difference in categorical variables and ANOVA was applied to compares means of weight, SBP, RR, DBP, SaO_2, HAS, PGA at each time point within each group using Bonferroni correction for multiple comparison. All statistical analyses were performed using SPSS software (version 22.0) and significance was set at $p < 0.05$ (two-sided) with 95% confidence interval.

Results

The children were statistically comparable with respect to the age, sex, gestational age and birth weight. Female preponderance was seen in either group with Male: Female ratio in group A being 1:4 and 1:3 in group B. No statistically significant abnormal antenatal developmental history was present in both the groups. 90% of children presented with IHs at birth in both the groups. Craniofacial region was the most commonly involved site in both the groups (50% in group A and 40% in group B). Baseline characteristics of the IHs (stage, type, depth, extent and presence of ulceration) are summarized in table 1. Group B had a greater number of children with red coloured IHs (65%) as compared to group A (25%). The mean age at which the intervention started was 11.5±18.1 months in group A and 14.64±39.18 months in group B.

The weight gain in both the group patients during the study period was adequate and comparable. Table 2 depicts inter-group comparison of HR, RBS, RR and SaO_2. All the variables were comparable and remained within normal range throughout the follow up. At 20^{th} follow up, Group A showed fall in DBP although it was in normal range (Table 3). SBP measurements throughout and DBP at rest of the follow ups were otherwise normal.

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Table 1: Baseline clinical characteristics of hemangiomas

Sr. no	Variable	Group A	Group B	p Value
1	Stage (progressive/plateau)	11/9 (55%/45%)	8/12 (40%/60%)	0.34
2	Type (Superficial/mixed)	15/5 (75%/25%)	16/4 (80%/20%)	1.0
3	Depth (Superficial/Mixed/Deep subcutaneous)	13/4/3 (65%/20%/15%)	15/2/3 (75%/10%/15%)	0.89
4	Extent (Localized/multifocal)	14/6 (70%/30%)	18/2 (90%/10%)	0.23
5	Color (Blue/Pink /Red)	0/15/5 (0%/75%/25%)	1/6/13 (5%/30%/65%)	0.01*
6	Ulcerative nature(no/yes)	17/3 (85%/15%)	19/1 (95%/5%)	0.60

Table 2: Clinical parameters: HR, RBS, RR, SaO_2

	HR			RBS			RR			SaO_2		
Time of measurement	Group A	Group B	p-value	Group A	Group B	p-value	Group A	Group B	p-value	Group A	Group B	p-value
Baseline	107±11	110±10	0.43	95±6	93±5	0.18	42±8	42±6	0.87	99±1	99±1	0.49
4 weeks	107±11	110±10	0.41	91±7	96±14	0.17	39±7	39±7	0.90	99±1	99±1	0.49
8 weeks	106±10	108±9	0.50	95±5	93±5	0.18	39±8	39±7	0.74	98±1	99±1	0.27
12 weeks	105±9	107±7	0.42	95±7	0.7697±6	0.17	37±7	38±7	0.70	98±1	98±2	0.15
16 weeks	103±7	106±7	0.33	98±5	97±7	0.69	37±7	38±7	0.70	98±1	100±1	0.54
20 weeks	107±11	110±10	0.37	98±6	98±6	0.88	37±7	38±6	0.74	98±1	99±1	0.46
24 weeks	104±8	108±8	0.34	97±5	99±5	0.11	36±7	36±6	0.70	99±1	100±1	0.65
28 weeks	103±3	104±7	0.70	98±6	96±5	0.30	35±7	35±6	0,65	98±1	99±1	0.39
32 weeks	100±6	101±6	0.71	98±5	100±5	0.46	32±7	34±6	0.34	99±1	99±1	0.65
36 weeks	97±4	97±5	0.80	96±7	94±6	0.40	31±7	34±6	0.16	98±1	99±1	0.39
18months	87±5	88±5	0.56	100±10	95±10	0.13	25±5	27±4	0.09	99±1	99±1	0.49

Table 3: Clinical parameters: SBP and DBP

	SBP			DBP		
Time of measurement	Group A	Group B	p-value	Group A	Group B	p-value
Baseline	112±5	112±6	0.87	72±4	73±3	0.53
4 weeks	113±3	113±5	0.73	73±3	72±3	0.13
8 weeks	113±4	112±4	0.79	72±2	72±3	0.30
12 weeks	114±4	113±4	0.50	73±3	73±3	0.45
16 weeks	113±4	114±6	0.21	71±2	72±3	0.51
20 weeks	111±5	111±5	0.73	71±3	73±2	0.007*
24 weeks	112±4	112±5	0.95	73±3	73±3	0.08
28 weeks	112±3	114±3	0.22	73±3	73±3	0.90
32 weeks	111±6	112±4	0.70	73±3	72±3	0.46
36 weeks	112±5	111±6	0.56	72±3	72±3	0.19
18months	111±5	113±5	0.13	73±3	72±3	0.30

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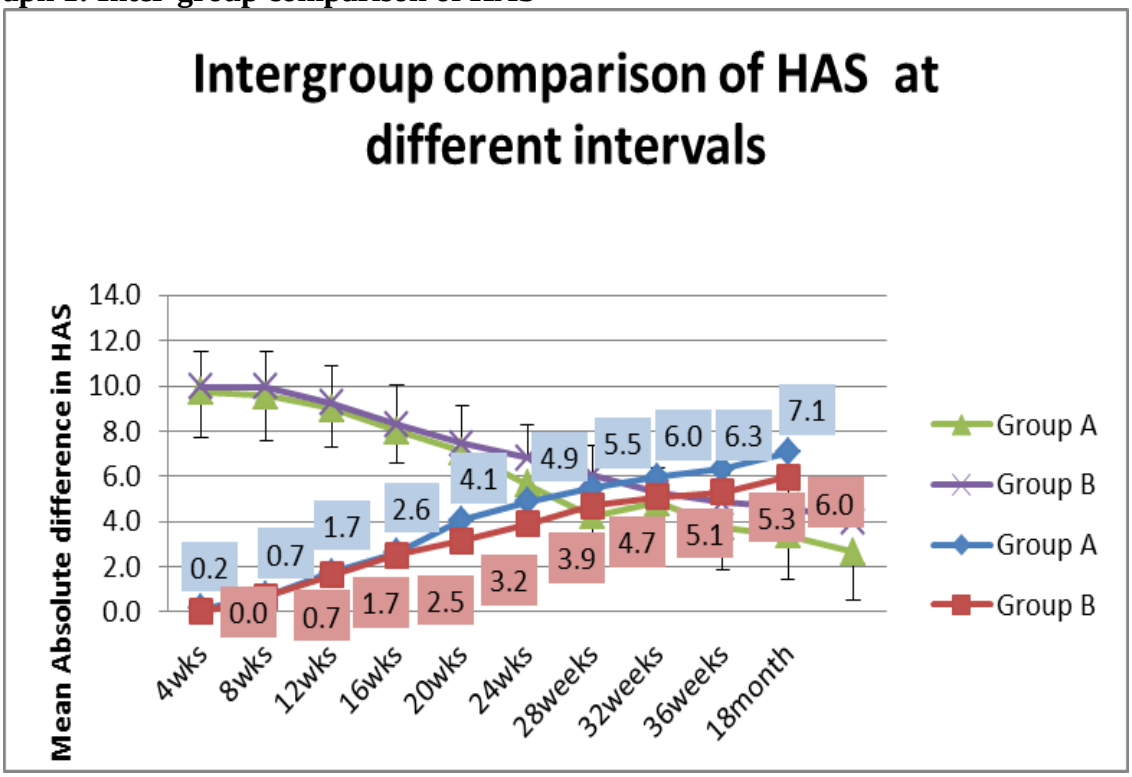
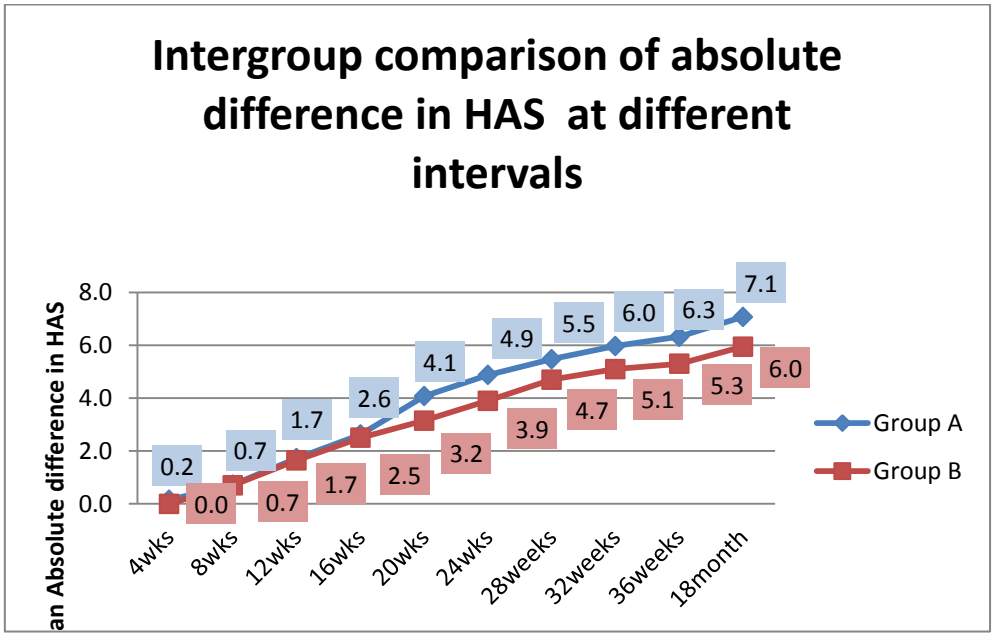
The primary outcome variable i.e HAS showed statistically significant decline among patients on oral propranolol at 20th week and later on (p-value 0.02, 0.01, 0.02, 0.03, 0.02 and 0.02 at 20th, 24th, 28th, 32nd, 36th weeks and 18th months respectively) (Graph 1). It was also observed that the absolute difference in HAS from baseline was statistically significant in both the groups at 28th and 32nd weeks with a p value of 0.015 and 0.015 respectively (Graph 2).

Graph 1: Inter-group comparison of HAS



Graph 2: Absolute difference in HAS from the baseline



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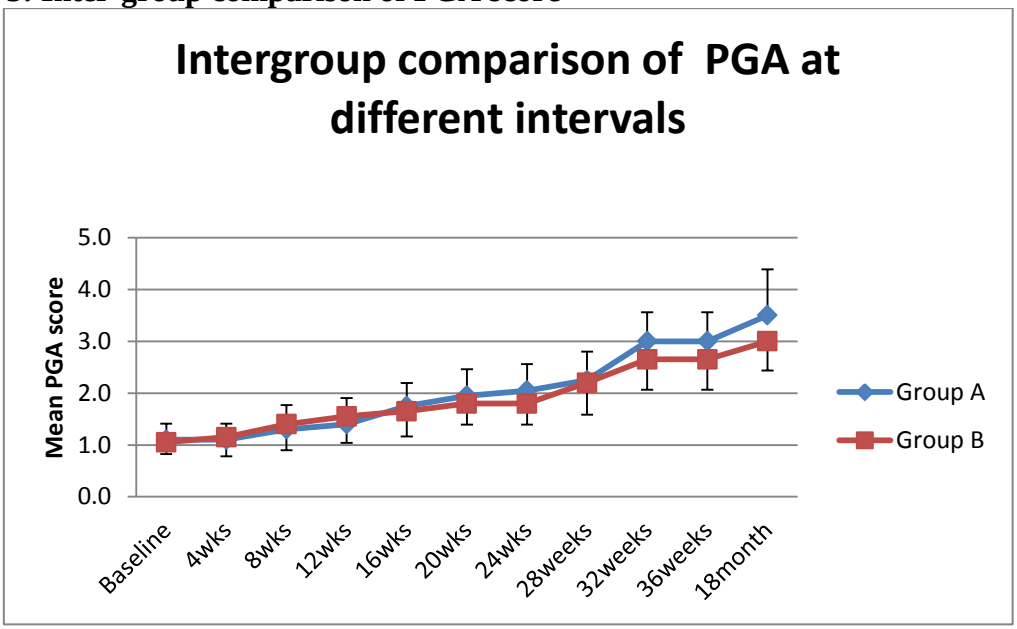
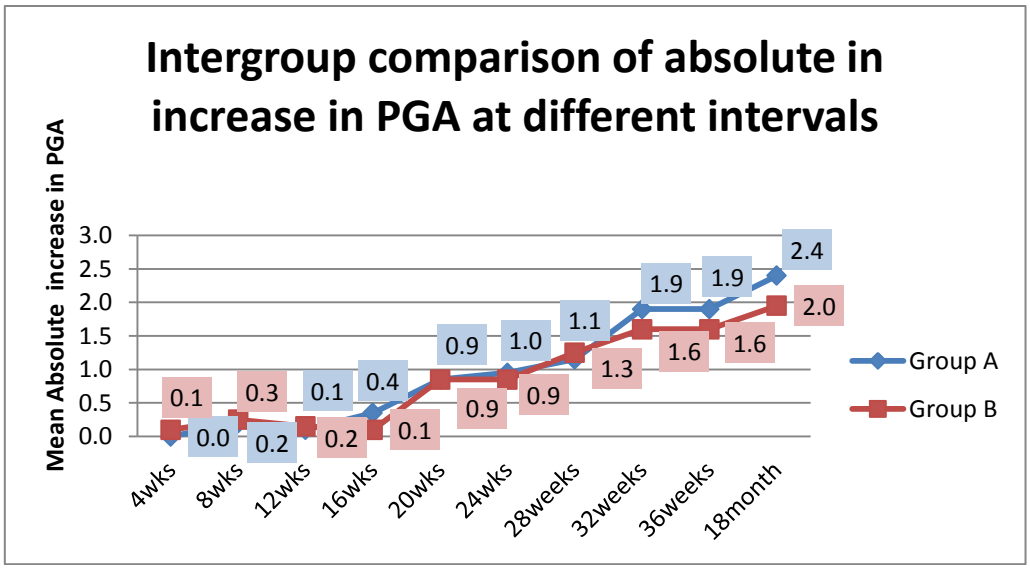
The gain in the PGA score was more in Group A patients and was statistically significant on final follow up i.e. at 18 months (p-value 0.04). Absolute difference from the base line was also significant among propranolol patients (p-value 0.04) (Graph 3 & 4).

Graph 3: Inter-group comparison of PGA score



Graph 4: Absolute difference in PGA score from the baseline



Discussion

Although both oral propranolol and topical timolol have been accepted well in the treatment of superficial infantile hemangiomas, little data is present in the literature as which drug should be preferred. Our study intended to compare clinical efficacy of these two treatment modalities. All the baseline characteristics of the IHs in the study population were comparable except for the colour; Group B patients were having higher red coloured IHs. These lesions are three to five times more common in females [13, 14]. Similar results were noted in our study, wherein female patients were 80% and 70% in Group A and Group B respectively. Mean gestational age was 35 weeks in either group and the findings were in

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concordance with the result obtained by Rodriguez et al who reported that the infantile hemangioma occur more commonly among preterm neonates [13].

These lesions are known to occur since birth as studied by Holland et al. 90% of our babies in both the groups gave similar history [15]. IHs is commonly seen in low birth weight children [16]. However, in the present study mean birth weight (in kg) was 2.39±0.35 and 2.31±0.40 in Group A and Group B respectively. Overall, 80% of cutaneous hemangiomas are single and 20% of the lesions are multiple in numbers [14]. 70% of our children in group A and 90% in group B reported with single vascular lesion. Proliferating IHs are often warm to palpation and seem to be of little concern to the affected infant unless they are ulcerated. In one series, 62% of observed IHs were superficial, 15% were deep, and 23% were mixed [4]. Here, in group A; superficial, deep and mixed lesions were 65%, 15% and 20% and in group B; superficial, deep and mixed IHs were 75%, 15% and 10% respectively.

Therapeutic options for the treatment of infantile haemangioma include intra-lesional injection of steroids, systemic steroids and immune-modulators but due to the significant adverse effects and differences in their therapeutic efficacies; these treatment modalities are now being disfavoured [6, 15, 18]. Recently, role of oral Propranolol has been studied extensively and it has replaced oral corticosteroids as the therapy of choice due to its better clinical effectiveness and safety. Propranolol, as a non-selective β-blocker could suppress growth of IHs by inducing vasoconstriction, angiogenesis inhibition and apoptosis induction. Recent studies have demonstrated that oral propranolol could achieve a satisfactory therapeutic response at a dosage of 2–3 mg/kg per day. In the present study, we applied propranolol at a dosage of 2 mg/kg per day with an effective response rate of 97% which is consistent with the results (96–98%) by Leaute-Labreze et al [8].

As for topical drug therapy, diverse formulations of timolol including timolol 0.1% gel, timolol 0.25% gel forming solution, timolol 0.5% eye drop, timolol 0.5% gel forming solution and timolol 0.5% gel have been attempted for the treatment of superficial His [9]. In a previous study, topical timolol maleate 0.5% hydrogel was applied for treating superficial IHs and it was discovered that topical timolol could achieve a satisfactory clinical responses with mild side effects [14, 18]. Propranolol and timolol are both β-blockers, which may regulate the growth of IHs in a similar way. Sultan et al in a recent study evaluated the clinical efficacy and adverse effects of oral propranolol in comparison with topical timolol for the treatment of IHs and obtained enhanced clinical response with oral propranolol than the topical timolol formulation [14]. Contrasting results were obtained in a study by Wu et al, depicting superior therapeutic efficacy of timolol over propranolol [18]. The current study found that both systemic beta blocker propranolol and topical timolol achieved a satisfactory therapeutic efficacy in the treatment of IHs in the initial phase. However, oral propranolol when compared to topical timolol had significant improvement in therapeutic efficacy (p value <0.05) especially after 20 weeks of therapy.

Several scoring systems for infantile haemangioma have been described over the years to evaluate the clinical response during the follow-ups. Hemangioma activity score has been considered superior with two major advantages. Firstly, it can be used both prospectively (on patients) and retrospectively (on clinical photographs). Secondly, it reflects the rapid effect of the treatment with expected change in the score [19]. In the current study, HAS and PGA were calculated at baseline and then at every follow-up for assessing the improvement in size, colour and ulceration along with vital clinical parameters including RR, SaO_2, HR, BP and RBS to look for any adverse effects of the applied intervention in either group.

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In the current study, both drugs were therapeutically efficacious as denoted by the HAS and PGA scores. The baseline HAS and PGA scores in both the groups were statistically comparable. The HAS score in the propranolol group reduced from 10±2 at baseline to 3±2 at the end of 18 months whereas the reduction in the timolol group was from a baseline HAS score of 10±2 to 4±1 at the end of 18 months. The overall absolute change in the HAS score at the end of treatment in the propranolol group was 7.0±2.7 and 5.95±1.40 in the timolol group and overall percentage improvement in the HAS score was 72% and 60% in the propranolol group and timolol group respectively. The PGA score increased from a baseline score of 1±0.3 to 3±0.9 in the propranolol group and 1±0.2 to 3±0.6 in the timolol group. Thus, both the drugs improved the HAS and PGA scores effectively. On further analysis and comparison of the therapeutic efficacy of the treatment given in each group, the HAS score was statistically significant at 20, 24, 28, 32, 36 weeks and later at 18 months with a p value of 0.02, 0.01, 0.02, 0.03, 0.02 and 0.02 respectively. The HAS score obtained was significantly better (p value <0.05) in the propranolol group. The absolute decrease in the HAS from the baseline was higher and statistically significant in the propranolol group at 28 and 32 weeks with p value of 0.015 and 0.015 respectively. The PGA score when compared between the two groups was statistically significant at 18 months (p value <0.05); with higher scores in the propranolol group. In the current study, systemic propranolol was therapeutically more efficacious than topical timolol for the treatment of IHs particularly in the later period.

McMohan et al did not observe much improvement in children with haemangiomas in whom the treatment was started after 9 months of age. Most of the lesions would have proliferated well by then [20]. However in our study, there was no significant difference between the response and age (months) of initiation of the therapy among both the groups. Common adverse effects of propranolol include sleep disturbance, cold hands and feet, diarrhoea, and bronchial hyper-reactivity. Rare adverse effects include bradycardia and hypotension which are generally asymptomatic. Severe hypoglycaemia may be associated with decreased responsiveness or seizures [7]. No significant drug adverse events other than fall in DBP (p value <0.05) in the propranolol group at 20 weeks was observed. Both the drugs were found to be safe even when used at the higher dosages.

We tried to compare both oral propranolol and topical timolol on IHs effectively with multiple clinical variables including two widely accepted scoring systems but still certain limitations exist in our study in the form of few patients in each group and presence of higher number of children with red IHs in the timolol group which could have been a factor in lower therapeutic efficacy of timolol as compared to propranolol.

Conclusion

We conclude that both oral propranolol and topical timolol are equally safe in the treatment of superficial infantile hemangiomas. However, promising results are obtained with oral propranolol therapy especially with its long term usage.Therefore, it should be considered as the first line beta-blocker therapy in the management of superficial infantile hemangiomas. A study incorporating a larger group of patients is suggested for a better comparison between these two drug modalities.

Conflict of interest

Nil

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