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ORIGINAL ARTICLE

Comparison of Effectiveness of Propranolol with Prednisolone in the Treatment of Infantile Hemangioma

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ABSTRACT

Objective: Multiple treatment modalities have been used to treat infantile hemangioma, among which oral prednisolone and propranolol are the leading one. Our objective was to conduct a randomized control trial to compare the outcome of both drugs.

Study Design: Randomized control trial was conducted on total of 56 patients, 28 in each group.

Place and Duration of Study: The study was conducted in the department of plastic and reconstructive surgery, Mayo Hospital, Lahore and the total duration was two years.

Material and Methods: After randomization, oral propranolol was given to one group in a dose of 2 mg/kg/day in three divided doses and oral prednisolone was given to the other group in the dose of 3 mg/kg/day as a single dose in the morning. Outcome after 6 months was measured in terms of percentage reduction in size and cosmetic outcome assessed by blinded plastic surgeon.

Results: Our results showed higher percentage reduction of size of the lesion in propranolol group as compared with the prednisolone group with p-value of 0.001 which is statistically significant. When assessed by the blinded plastic surgeons, propranolol group showed significantly higher satisfaction rate as compared with the prednisolone group (p-value = 0.033).

Conclusion: Oral propranolol is a better first line therapy as compared with prednisolone in the treatment of infantile hemangioma, in terms of percentage reduction in size of the lesion and surgeon's satisfaction.

Key Words: *Infantile hemangioma, Propranolol, Prednisolone, Outcome, treatment dosage*.

INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign vascular tumours of infancy and especially occur in 4-5% of white infants. They are approx. 3-5% more common in females. There is also an increased incidence of 23% in neonates weighing less than 1200 gm. These lesions occur 60% in head and neck region followed by torso (25%) and both upper and lower extremities (15%). They vary in size, extent, morphology and have a very unpredictable clinical course which correlates with its three stages of histological appearance, i.e. Proliferating phase (first 6-8

months of life), involuting phase (from 1-5 yrs. of age) and involuted phase (after 5-7 yrs. of age).[1]

Treatment options include observation of clinical course of the disease, medical therapies (corticosteroid, B-blocker, interferon and vincristine) and surgical therapies (including excision and primary closure, lasers and debulking). The plan of management for these patients depends on many factors which include tumour size, location, extent, physician comfort and personal experience with the different available modalities.[2]

Till recently, systemic (oral) corticosteroids were the current accepted standard of medical treatment and were considered as first-line medical therapy for problematic and life-threatening hemangiomas. Steroids are neither completely safe nor universally efficacious. Altered growth (6 percent) and moon facies (5 percent) are the most common side effects associated with steroid use. Other side effects include osteoporosis, hypertension, adrenal suppression and fungal infections. Rare complications include myopathy, cardiomyopathy, premature thelarche and hirsutism.

Propranolol is a relatively recent therapy of IHs with fewer side effects, a different mechanism of action, and greater efficacy than current first-line corticosteroid therapy. Interestingly this observed response was serendipitous, discovered with an attempt to treat the corticosteroid-induced hypertrophic cardiomyopathy in infants with very large hemangiomas.[3] The mechanism of action in shrinking IHs remains a mystery. Propranolol's effects on placenta have been demonstrated when used to treat pre-eclampsia. It is believed that propranolol induces constriction of affected vessels and also inhibit many angiogenic factors to induce vasoconstriction. Furthermore, it also enhances the apoptotic process of endothelial cells of blood vessels especially capillaries and selectively inhibits matrix metalloproteinase-9. This inhibition again supports the antiangiogenic properties of propranolol and explain its mechanism of action.[4]

Despite the fact that propranolol has some side effects but it can be argued that it is more efficacious and cost effective and has less significant side-effects than corticosteroids.[2] In fact propranolol is emerging as first line medical therapy for treating IHs.[5]

Contraindications for propranolol therapy include PHACE (posterior fossa malformations, hemangioma, arterial lesions, cardiac abnormalities/aortic coarctation, and eye abnormalities) syndrome, congenital heart diseases, aberrancies of cerebrovascular anatomy, asthma/reactive airways, blood glucose abnormalities.[6] Complications with this therapy include bradycardia, hypotension, hypoglycemia, seizures, rash, and bronchospasm. Generally, these complications are rare in the pediatric population and found with doses higher than 2 mg/kg per day.[7]

Multiple studies have been done for individual effects of corticosteroids and propranolol. A recent systemic review for all articles published for hemangioma treatment using corticosteroids and propranolol therapy has been done. Conclusive evidence for the superiority of propranolol is lacking and randomized controlled trials comparing the two treatment modalities are highly recommended.[8]

MATERIAL AND METHODS

In this study, the patients admitted to the department of Plastic Surgery, Mayo Hospital, Lahore with infantile hemangioma fulfilling the inclusion criteria were included. Inclusion criteria include threatening ulceration/distortion on any vital body part like eyelid, nose ear or lip, periorbital hemangiomas which can cause derivational amblyopia and any lesion with high parents' concerns not willing to wait for spontaneous resolution. Patients were randomly picked using random number table. Randomly picked up patients were divided into two groups: Group A (Receiving propranolol) Group B (Receiving Prednisolone). All the inclusive patients were updated with pre-medication bio data, complete clinical history was documented, clinical examination was done, consent was taken, counselling was done and clinical evaluation of lesion and standardized photographs were taken. Before initiating treatment, baseline vital signs including pulse and blood pressure, finger stick blood glucose, EKG, and echocardiogram were done. Patients with large segmental facial hemangiomas were

additionally advised facial/brain magnetic resonance imaging. A thorough evaluation by the attending pediatrician was done to determine contraindications for treatment [e.g., PHACE (posterior fossa malformations, hemangioma, arterial lesions, cardiac abnormalities/aortic coarctation, and eye abnormalities) syndrome, congenital heart disease, aberrancies of cerebrovascular anatomy, asthma/reactive airways, blood glucose abnormalities. After ruling out contraindications to propranolol and prednisolone, treatment was started on inpatient basis.

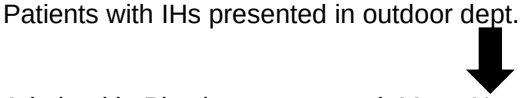
In group A, the treatment regimen was to administer propranolol 2 mg/kg per day divided in three doses and was continued until a plateau in improvement was seen or any of the complications of therapy were found. Vital signs were checked after the first dose administration and patients were kept in patient for three days. On discharge parents were given handouts regarding the warning signs of hypoglycemia, bronchospasm and hypotension. They were asked to immediately report to the hospital in case of any of the warning signs. Weaning of the medication was performed over 2 month's duration to minimize the risk of a hyper-adrenergic withdrawal response.[9]

In group B prednisolone was administered orally using a standardized protocol of 3 mg/kg given once daily as a single dose in the morning for 1 month, followed by a taper until the infant is 10 months of age. H_2 receptor antagonist Famotidine was added as gastro protective agent.[10] Drug was tapered earlier if side effects develop or no response was seen after 6 weeks. These patients were shifted to propranolol therapy and were excluded from the study. Size of the lesions initially and during follow up periods were measured using transparent graph paper and total area in centimeter square was compared.

During the total 6 months period of follow up and complete course of medication, clinical examination was done to assess regression of lesion according to the levels of reduction described and standardized photographs were taken to assess and compare the cosmetic outcome.

Research scheme

Patients with IHs presented in outdoor dept.



Admitted in Plastic surgery ward, Mayo Hospital, Lahore.

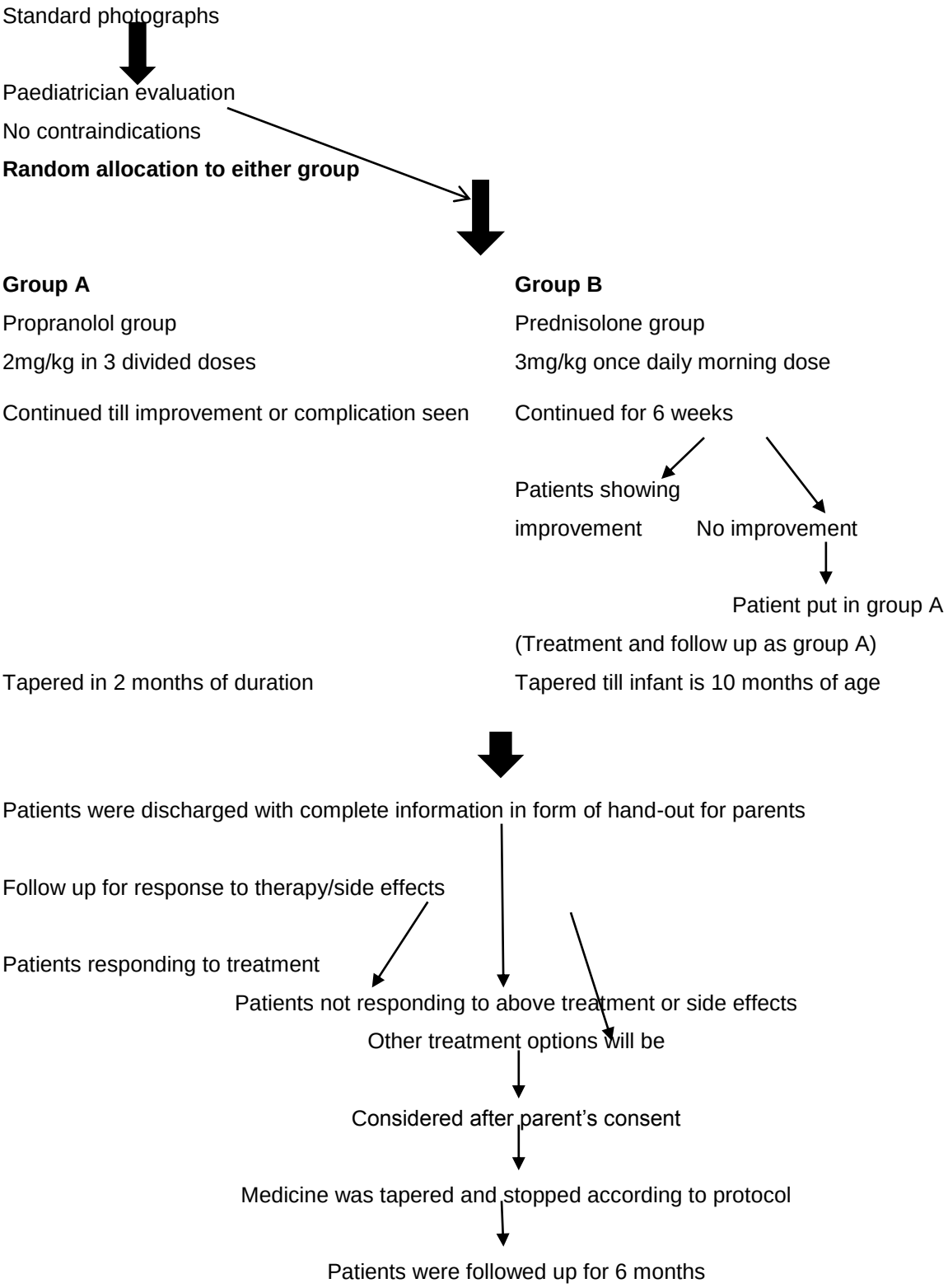
Patients fulfilling inclusion criteria inclusion picked up randomly

Didn't fulfil inclusion criteria

Workup started

Other treatment options e.g surgery

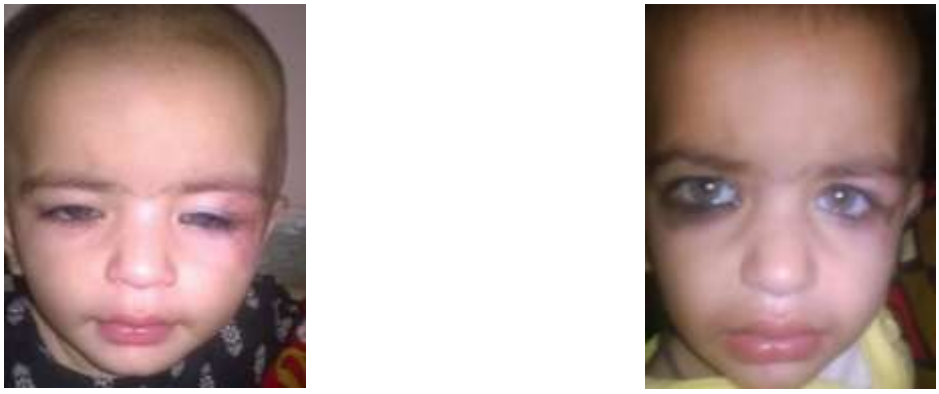
- Complete bio data
- Clinical history and examination (vitals)
- Clinical examination and evaluation of lesion
- Consent and counselling of parents
- Investigations i.e. BSR, EKG, echocardiogram, MRI (if indicated)


Standard photographs
Paediatrician evaluation
No contraindications
Random allocation to either group
Group A
Propranolol group
2mg/kg in 3 divided doses
Continued till improvement or complication seen
Tapered in 2 months of duration
Group B
Prednisolone group
3mg/kg once daily morning dose
Continued for 6 weeks
Patients showing improvement
No improvement
Patient put in group A
(Treatment and follow up as group A)
Tapered till infant is 10 months of age
Patients were discharged with complete information in form of hand-out for parents
Follow up for response to therapy/side effects
Patients responding to treatment
Patients not responding to above treatment or side effects
Other treatment options will be
Considered after parent's consent
Medicine was tapered and stopped according to protocol
Patients were followed up for 6 months

Standard photographs and measurements of the lesion were taken in both groups for comparison with premedication measurements and photographs at the end of 6 months follow up after completion of therap

Conclusion was made

Fig 1: Propranolol therapy pre and post treatment



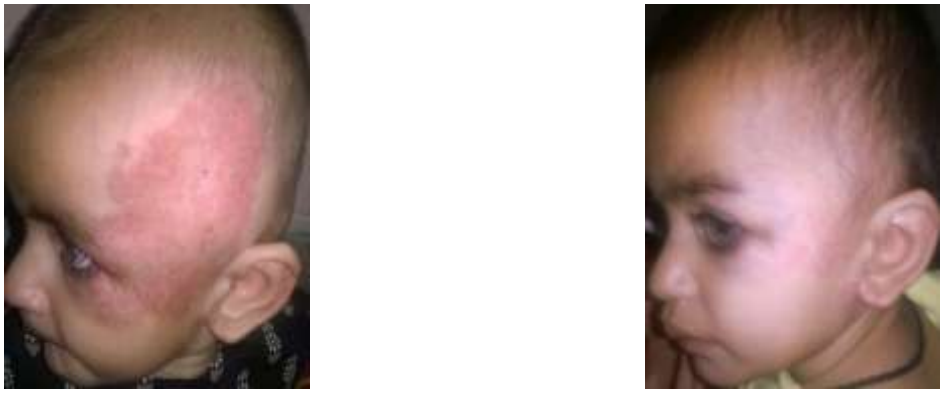


Fig 2: **Propranolol therapy pre and post treatment**

Fig 3: **Prednisolone therapy pre and post treatment**

RESULTS

TABLE 1: Comparison of gender (n=52)

Group	Gender		Total
	Male	Female	
Propranolol	11	17	28
Prednisolone	10	14	24
Total	**21**	**31**	**52**

Analysis: Total number of patients in propranolol group are slightly higher and there is also slight predominance of female gender in both groups

TABLE 2: Age statistics (n=52)

Group		Total number	Mean Age	Std. Deviation
Age (months)	Propranolol	28	6.32	2.45
	Prednisolone	24	5.96	3.33

Comparison of age between both groups shows no significant difference between the two groups

TABLE 3: Comparison of initial size (n=52)

	Group	N	Mean	Std. Deviation
Initial size (cm^2)	Propranolol	28	40.71	27.73
	Prednisolone	24	39.79	28.73

Comparing initial size of the lesion between two groups shows no significant difference

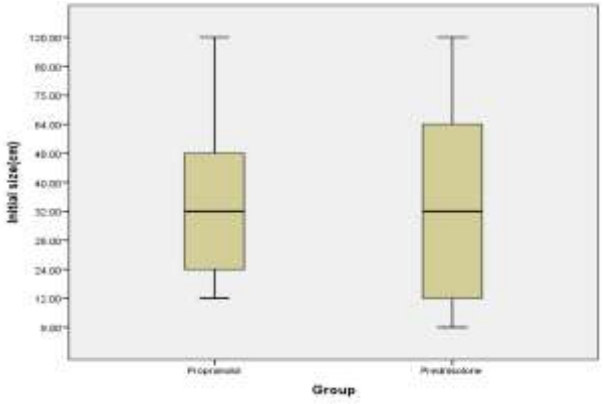


Fig 4: Comparison of Initial Size (n=52)

Figure shows that there is no signify cant difference in the initial size of both groups.

TABLE 4: Comparison of final size (n=52)

Group		N	Mean	Std. Deviation
Final size (cm^2)	Propranolol	28	8.16	4.87
	Prednisolone	24	12.75	8.04

Table shows that there is a significant difference in final size of the lesion of both groups

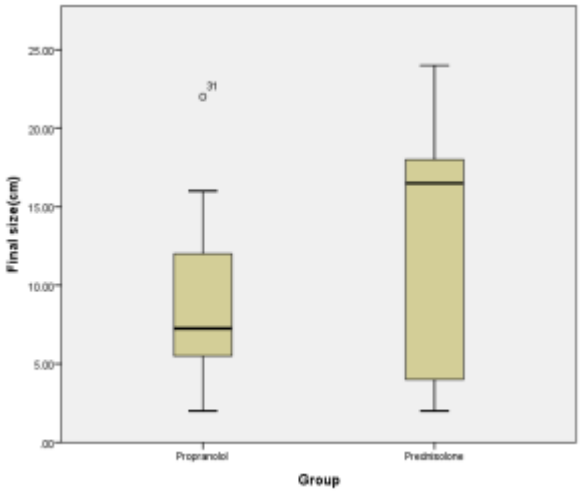


Fig 5: Final size comparison

Figure shows significant difference in the mean of final size of the lesion in both groups. Mean of final size of prednisolone group is significantly high than propranolol group.

TABLE 5: Comparison of percent reduction (n=52)

Percent Reduction					
	Group	N	Mean	Std. Deviation	p-value
Percentage reduction	Propranolol	28	77.43	9.05	0.001
	Prednisolone	24	65.67	14.53	

Table shows high percent reduction in propranolol group as compared with prednisolone group.

TABLE 6: Surgeon observation

Group	Surgeon observation		Total	p- value
	Satis-factory	Unsatis-factory		
Propranolol	24	4	28	
Prednisolone	14	10	24	0.033
Total	**38**	**14**	**52**	

P-value (0.033) shows significantly high surgeon satisfaction rate for propranolol group.

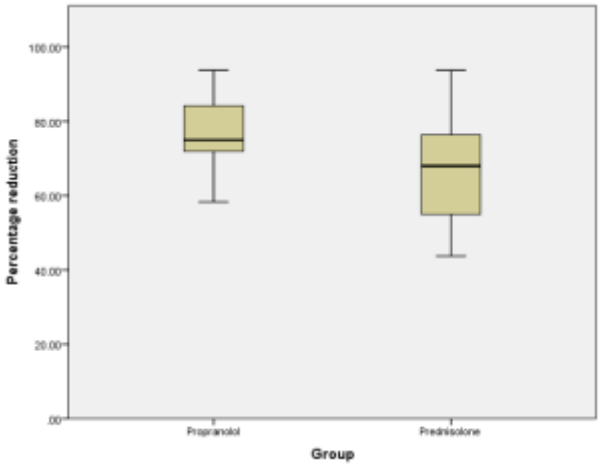


Fig 7: Percent reduction

Figure shows high mean percent reduction in propranolol group.

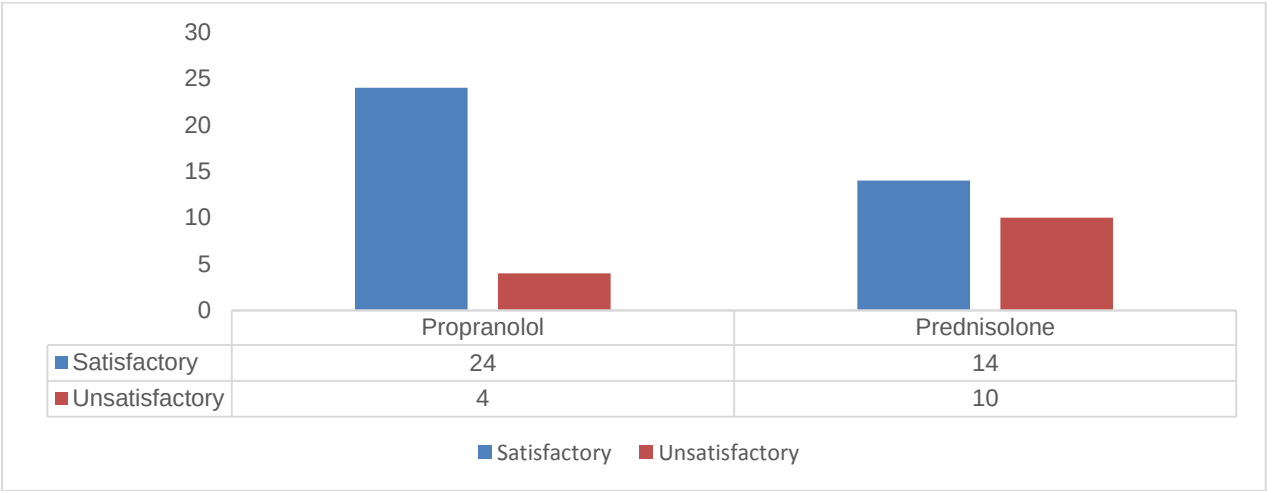


Fig 8: Surgeon observation

Figure shows high satisfaction rate of blinded surgeons for propranolol group as compared with prednisolone group.

DISCUSSION

We have conducted a randomized control trial comparing the efficacy of propranolol and prednisolone in the treatment of infantile hemangioma. Prednisolone has been used for a long period of time in the treatment of infantile hemangioma, however, the use of propranolol is quite recent and propranolol's popularity in the use of IH was remarkable. Uptill September 2010, only six series described its use in approximately 10 patients and by December 2011, number of patients increases to 1200.[11] Their role in the treatment of infantile hemangioma as first-line medical therapy is still controversial.

In our study, we randomized our patients into two groups, propranolol group and prednisolone group, and we concluded that propranolol group had markedly better outcome results as compared with the prednisolone group in terms of percent reduction in the size lesion and cosmesis. This difference in outcome can also be judged by the compliance of the treatment in propranolol group. All the 28 patients in propranolol group completed their treatment course, however, in prednisolone group 4 patients lost their follow up and were excluded from the study as shown in table 1.

Comparing both groups in our study, propranolol group showed better outcome in terms of percentage reduction in size as compared with the prednisolone group i-e 77.43% and 65.67% respectively and better satisfaction of blinded plastic surgeon in terms of cosmesis as evident in table 5 and fig 7.

In a very recent single center RCT, the author concluded the non-inferiority of propranolol over prednisolone in the treatment of IH.[12] The positive aspect of this study was that the author uses MRI scan to determine the pre and post treatment volume of the lesion, which is the gold standard to assess the full extent of the lesion. But due to high cost of the modality we could not be able to perform in our patients. Comparing our study with another recent meta-analysis demonstrated a resolution rate of 97% in propranolol group versus 71% for systemic corticosteroids. In another study, results showed 91% accumulative success rate for refractory cases after steroid therapy and 98% for patients treated with propranolol therapy.[13]

If we look at the safety profile of both drugs, literature suggests that the complication rate of steroid therapy is more than double when compared with propranolol (23% versus 9.6%).[14] Though the dosage used in our study for both the groups was low for their complications. We used 2 mg/kg/day in 3 divided doses of propranolol and most of the complications reported after propranolol use are either at higher dose or intravenous administration. Similarly, dose of prednisolone 3 mg/kg/day was lower.

Boon et al. in his study suggest that if we stop the steroid medication for two weeks, the growth-height curve of the subject returns to normal.[15] Hence it is possible that to complete the full course of steroid therapy for infantile hemangioma, which may last up to six months, we may have to put our patient on multiple sessions of therapy.[16] Also the patient is always under threat of complications due to long term treatment of steroids. In contrast, propranolol treatment needs most of its attention in pre-medication workup and monitoring. Patient should be observed closely and important parameters regarding the drugs like blood pressure, heart rate and glucose levels should be monitored. Dosage needs to be adjusted and lowered if mean blood falls below 50 mmHg, heart rate below 90/min and blood sugar level below 72 mg/dl. Therefore, it is highly recommended that before initiation of propranolol therapy, patient should undergo thorough clinical evaluation from a pediatrician and cardiologist after proper vital monitoring and investigation. Investigations may include electrocardiogram, echocardiogram, chest X-ray when indicated[17,18]

According to some studies, the deeper parts of the lesion respond better to propranolol therapy whereas steroid therapy is more effective in regression of the superficial components.[19] This would suggest using propranolol as an effective adjunct to corticosteroid therapy. However, we did not employ this form of dual therapy in our current study. It is pertinent to note that contrary to local corticosteroid therapy that has been an integral part of haemangioma treatment for years, it is only systemically administered propranolol that has proven to be of benefit and carved a niche in haemangiomal regression.

Propranolol has been postulated to alter the course of proliferation in haemangiomas by inducing vasoconstriction and down regulating angiogenic factors like basic fibroblast growth factor and vascular endothelial growth factor.[20] Concomitantly, it enhances the process of apoptosis especially in capillary endothelial cells. Its antiangiogenic properties are further compounded by it being a selective inhibitor of matrix metalloproteinase-9. Propranolol has inherent beta-receptor blocking properties. These observations and the clinical success of propranolol in treating hemangioma imply that beta adrenergic pathways play a critical role in both the angiogenesis and progression of hemangiomas.[21] However, recurrence of the growth phase has been reported on cessation of therapy in some cases. One of the studies insinuates that propranolol allows regressed hemangiomas to maintain their status quo rather than inducing their involution.[22]

Our study is not free of limitation and drawbacks. It is very subjective to assess the effect of treatment on cutaneous lesions, which can affect the outcome. The ideal modality to access the pre and post treatment outcome was MRI scan which due to high cost was not possible in our setup. Another limitation of this study is that we yet have to quantify the exact minimum dose of both propranolol and prednisolone to give maximum outcome. Studies should be conducted to compare the effectiveness of propranolol in different doses with appropriate follow-up and strict complication monitoring.

In our trial sample size was low to provide strong evidence of safety profile of both drugs. However, according to a recent meta-analysis, the most commonly reported side effects of steroid use were altered growth and moon facies, and there is approximately 17.6% of incidence of overall side effects. Similarly, common side effects reported with the use of propranolol were hypotension, bradycardia and hypoglycemia and it was reported that approximately 13.7% of patients experience adverse effects with propranolol use. Incidence of complications varies according to the definition of complication by various studies. So, physicians have to take clinical decision keeping in mind the complication rate and safety profile of each drug.

Atenolol might me an alternative of propranolol, anticipating better safety profile and less neurocognitive issues caused by the use of propranolol.[23] Though there was little published data regarding the use of atenolol in the treatment if IH at the time this trial was ongoing, several studies have since been reported.[23-25] These publications have documented decreased risk of respiratory adverse effects and hypoglycemia because of the selective b-1 blocker activity of atenolol. Moreover, atenolol also decreases the central nervous system related side effects.[23-24] However, its use in the treatment of IH is lacking and further studies on its use in the treatment of IH are needed.

CONCLUSION

Propranolol is a better medical therapy for the treatment of infantile hemangiomas compared with corticosteroid in terms of better clinical outcome and fewer side effects. Due to its utility in the treatment of infantile hemangiomas, we got better understanding of its mechanism of action and therapeutic index. This randomized control trial suggest that prednisolone should replace propranolol as the first line treatment modality for problematic infantile hemangiomas. However, further trials are required to evaluate and compare the long-term effects of propranolol and to determine the safest and effective dose.

Conflict of interest:

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