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Original Research Article

Is Steroids in Infantile Hemangioma: An Unnecessary Evil?

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ABSTRACT

Aim: To compare the efficacy of propranolol alone versus a combination of propranolol and steroids in inducing regression of hemangiomas.
Methods: 3- groups were made. Oral Propranolol was given in incremental dosage for duration of 6 months. Oral Prednisolone was given and then tapered over 10weeks period. 3rd group was control group. Vitals (Blood Pressure, Pulse Rate and Blood glucose level), measurement and color of the lesion were checked at every visit or change of medication dosage.
Result: Maximum reduction of (69.5% versus 42.9%) in length and (72.4% versus 38.2%) in width was seen in patients receiving propranolol alone. Even though, there were statistically significant variations observed in the Systolic BP, Diastolic BP, Pulse rate and Blood Glucose level but clinically the variations were not significant. There were no major side-effects and impact of the medications on the vital parameters in each group. In control group, there was 10% and 12.6% mean reduction in the length and width of the lesion respectively during study period. Color reduced to light red color in 58% of patients and 26% of patients just had mild discoloration.
Conclusion: Propranolol alone is safe, superior and more effective in treating IH compared to the traditional first-line oral corticosteroid treatment. We can avoid the unnecessary serious adverse-effects of the steroids in small children.

Keywords: Side effect, Lesion, IH

INTRODUCTION

Infantile hemangioma (IH) is the benign pediatric vascular tumor. It is the most common soft tissue tumor of infancy with an incidence of 5% - 10% in all children less than 1 year of age. Infantile hemangiomas are diagnosed by their clinical history and examination. The treatment of IH depends on the type of hemangioma, stage, location, extent, number and distribution of the lesion, systemic involvement and presence or absence of any complications. There are many treatment options out of which the conventional approach is systemic corticosteroids. Intralesional and topical steroids were found useful in small and superficial hemangiomas only. [1]

It was observed serendipitously that Propranolol, a non-selective β- adrenergic receptor blocker, commonly used for cardiologic indications, was well tolerated and can control the growth of IH efficiently. [2] The usual starting dose for prednisolone is 2 to 3 mg/kg per day in two divided doses. [3,4] Even with high dosages of systemic steroids, response was seen in around 30-60% cases with incomplete regression in most of them. Glucocorticoids cause side effects which are very well

known. Short-term side-effects are more likely to develop with higher doses which may resolve after drug stoppage.

There are many studies either prospective or retrospective and many randomized controlled trials done in past comparing the efficacy, adverse effects, duration of therapy and success rates between corticosteroids and Propranolol. [5,6] Old studies, [1,7] never took the drug combination. In 2013, [8] there was a study on 30 children, where they took a combination of the drugs but did not compare it with control/ placebo drug (as it is said that in Involuted phase complete regression is seen by 10-12 years of age). They also didn't compare the reduction in size individually and discoloration of the lesion. We conducted this study from 2014 to determine the efficacy of Propranolol versus a combination of propranolol and steroids in inducing regression of hemangiomas and individualizing their effects and adverse-effects and also comparing it with a placebo drug.

MATERIALS AND METHODS

This was an observational correlation type of study. This study was conducted in the department of paediatric surgery, Sudhamayi group of hospitals and clinics, Kochi, Kerala.

Duration of the Study: This study was done using data collected from January-2014 to Decemer-2016 for a period of 2 years 5 months.

Study Population: The study group consisted of all children presenting to the paediatric surgery department with infantile hemangioma with the age ranging from 1 month to 10 years. All patients underwent detailed history, complete physical examination, photography of the lesion, Ultrasonography of the abdomen (to rule out any visceral hemangioma), electrocardiographic evaluation and vitals (pulse rate, blood pressure and blood glucose level) before admission. Total 50 patients were included in the study. 20 patients (Group 1/A) were given both corticosteroid and propranolol. Group 2/B also has 20 patient and they were given only Propranolol. 10 patients were included in Group 3/C, which is a control group. We excluded the children from this study who were having history of Asthma, Diabetes, Hypertension, Hypotension, Hypoglycemia, Liver Failure and Hemangioma with previous surgery, Visceral Hemangioma and Previous medical treatment for Hemangiomas.

Study protocol: Concurrence was taken from the chairman, academic committee, scientific committee and ethical committee for the study. Informed consent was taken from guardians for photography of the lesion, imaging and electrocardiographic evaluation.

Medication dosage protocol: Every child was admitted for observation. Medicines were started, after taking the informed consent from parents. If there is no fall in pulse rate and if blood glucose level is also normal, then after 72 hours of observation, patient will be discharged. Rest of the treatment will be continued at home. Patients will be reviewed in OPD.

Procedure: Propranolol was given at starting dose of 0.5mg/kg/day in 2 divided doses. After 2weeks, dose will be increased to 1mg/kg/day in 2 divided doses for 2weeks, provided pulse rate is within normal limits. Then 2mg/kg/day in 2 divided doses for 2 weeks, followed by maximum dose of 3mg/kg/day or maximum tolerable dose in 2 divided doses for 6 months. Vitals (blood pressure, pulse rate, blood glucose level) measurement and color of the lesion will be checked on every increase in medication dose and also at every visit.

Prednisolone was given with the starting dose of 2mg/kg/day in 2 divided doses for 4weeks, then 1mg/kg/day in 2 divided doses for 4weeks and then 1dose for 2 weeks and then stop. Vitals (blood Pressure, pulse rate, and blood glucose level) measurement and color of the lesion will be checked on every change in medication dose and also will be checked at

every visit. In between revisits in OPD, vitals (pulse rate, blood pressure and blood glucose level) will be checked every 2 weeks in a near-by hospital.

Statistical Methods: The data collected was entered into Microsoft excel spreadsheet and analysed using IBM SPSS Statistics, Version 22 (Armonk, NY: IBM Corp) were used for analysis of the data and Microsoft word and Excel have been used to generate graphs and tables etc. Descriptive and inferential statistical analysis has been carried out in present study. Descriptive data were presented in the form of frequency, percentage, mean, median, standard deviation and quartiles. Comparisons of the categorical variables between the study groups were performed using the chi-square test and fisher exact test. Variations in the lesion length and width over different time intervals in each group were compared using Friedman test followed by Wilcoxon sign rank test as well as ANOVA test.

RESULTS

The study group comprised of 50 patients, out of which 26 % were males and 74 % were females. In all the 3 groups, female predominance was seen with Male: Female ratio being 1: 2.8. In Group 1, the age and weight ranged from 3- 24 months and 2.3-12.2kg with median of 5.50 and 6.50 respectively. In Group 2, it was between 2-96 months and 4.6-31.5kg with median of 8.00 and 8.65 respectively. In Group 3, the age and weight varied between 1-24 months and 2.04-10 kg with a median of 7.50 and 6.65 respectively.

In this present study, it was seen that there was a significant reduction in the length of the hemangiomas over the study period of 6 month in all the 3 groups. During the 8th week, 4th month and 6th month, there was a significant difference between each group as seen in Table 1. On the pairwise comparison, it was observed that in Group 1 vs. Group3, length of the hemangiomas was not significantly deferring in the 8th week, 4th month and 6th month, but was significantly deferring in the Group 1vs. Group 2 and Group 2 vs. Group 3.

Table 1: Comparison of lesion length between the study groups at different time interval

Length (cm)	Group 1(N=20)		Group 2(N=20)		Group 3(N=10)		Kruskallwallis test	
	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	Chi square value (df)	p-value
Base	2.75 (2.49)	2.00 (1.50-3.00)	2.76 (2.02)	2.00 (2.00-2.90)	2.00 (0.78)	2.00 (1.75-2.63)	0.82(2)	0.66(NS)
2 week	2.46 (2.06)	1.80 (1.40-2.58)	2.25 (1.64)	1.75 (1.50-2.18)	2.00 (0.78)	2.00 (1.75-2.63)	0.73(2)	0.69(NS)
4 week	2.27 (1.92)	1.70 (1.30-2.50)	1.90 (1.43)	1.45 (1.23-1.85)	1.94 (0.74)	2.00 (1.60-2.58)	2.16(2)	0.34(NS)
6 week	2.07 (1.85)	1.50 (1.20-2.00)	1.54 (1.22)	1.15 (1.00-1.48)	1.83 (0.76)	1.80 (1.55-2.43)	4.27(2)	0.12(NS)
8 week	1.86 (1.75)	1.35 (1.00-1.90)	1.21 (1.02)	0.80 (0.80-1.17)	1.83 (0.76)	1.80 (1.55-2.43)	7.62(2)	0.02*
4 month	1.69 (1.58)	1.20 (1.00-1.50)	0.96 (0.95)	0.60 (0.50-0.88)	1.79 (0.71)	1.80 (1.55-2.20)	13.76(2)	0.001*
6 month	1.57 (1.49)	1.05 (1.00-1.40)	0.84 (0.85)	0.50 (0.43-0.88)	1.74 (0.67)	1.80 (1.55-2.20)	15.08(2)	0.001*
Chi square value (df)#	110.93(6)		118.55(6)		45.52(6)			
p-value	<0.001*		<0.001*		<0.001*			

#Friedman test

Baseline widths in all the 3 groups were not significant and so were comparable. Till the 2nd week, in all the groups, there was no significant change in the width but after that there was a significant variation in the width of the hemangiomas (as seen in table 2). On the Pairwise comparison, there was a significant variation in the width of the hemangiomas in Group 1vs. Group 2 and in Group 2 vs.

Group 3, but no significant difference in the width was observed in Group 1 vs. Group 3 till 8th week and after that it was significantly deferring.

In the present study (as seen in table 3), it was observed that there was significant variation in the systolic BP in each group throughout the study period. Even though, it was statistically significant but clinically the variation was not significant. There was no major side-effect and impact of the medications on the systolic blood pressure in each group. It was observed that there was no significant variation (p value ->0.05) when the change in systolic BP at each time interval between the study groups were compared. Similar results were reported for diastolic BP (table 4) and glucose level (table 5). It was observed that there was no significant variation (p value >0.05) when the change in blood glucose level at each time interval were compared between the study groups.

Table 2: Comparison of lesion width between the study groups at different time interval

Width (cm)	Group 1(N=20)		Group 2(N=20)		Group 3 (N=10)		Kruskallwallis test	
	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	Chi square value (df)	p-value
Base	2.85 (1.61)	2.00 (2.00-3.00)	2.61 (1.02)	2.15 (2.00-3.00)	2.60 (0.94)	3.00 (2.00-3.00)	0.75(2)	0.68(NS)
2 week	2.70 (1.67)	1.90 (1.80-2.77)	2.14 (0.87)	1.80 (1.60-2.60)	2.60 (0.94)	3.00 (2.00-3.00)	5.61(2)	0.06(NS)
4 week	2.47 (1.48)	1.80 (1.72-2.50)	1.72 (0.75)	1.45 (1.20-2.00)	2.51 (0.92)	2.70 (2.00-3.00)	9.47(2)	0.009*
6 week	2.28 (1.42)	1.80 (1.53-2.28)	1.45 (0.70)	1.10 (1.00-1.80)	2.41 (0.86)	2.70 (1.95-2.75)	12.28(2)	0.002*
8 week	2.09 (1.32)	1.60 (1.43-2.00)	1.15 (0.62)	0.85 (0.70-1.50)	2.35 (0.88)	2.60 (1.78-2.75)	16.65(2)	<0.001*
4 month	1.89 (1.24)	1.50 (1.43-1.80)	0.85 (0.54)	0.60 (0.43-1.15)	2.29 (0.81)	2.50 (1.78-2.73)	24.48(2)	<0.001*
6 month	1.76 (1.15)	1.50 (1.08-1.60)	0.72 (0.45)	0.50 (0.40-1.05)	2.27 (0.82)	2.50 (1.80-2.73)	26.35(2)	<0.001*
Chi square value (df)[#]	113.71(6)		119.38(6)		47.08(6)			
p-value	<0.001*		<0.001*		<0.001*			

[#]Friedman test

Table 3: Comparison of systolic blood pressure between the study groups at different time interval

Systolic Blood Pressure (SBP)	Mean (SD)			ANOVA	
	Group 1(n=20)	Group 2(n=20)	Group 3(n=10)	F-value	p-value
Base	91.20 (5.05)	98.10 (8.22)	91.20 (6.81)	6.14	0.004*
2 week	84.95 (4.94)	95.10 (8.91)	90.00 (7.42)	9.82	<0.001*
4 week	88.30 (4.56)	96.80 (8.09)	89.00 (7.38)	9.10	<0.001*
6 week	89.20 (4.37)	97.30 (9.16)	89.00 (7.38)	7.69	0.001*
8 week	88.80 (3.40)	96.60 (9.89)	89.40 (7.06)	6.48	0.003*
4 month	88.70 (3.63)	96.40 (9.94)	89.40 (7.06)	6.13	0.004*
6 month	88.50 (3.66)	96.10 (9.44)	89.40 (7.06)	6.33	0.004*
F value(df1,df2)[#]	14.52(2.85, 54.15)	1.71(1.72, 32.65)	5.84(2.41,21.66)		
p-value	<0.001*	0.20(NS)	0.007*		

[#]Repeated Measures ANOVA

Table 4: Comparison of diastolic BP between the study groups at different time interval

Diastolic Blood Pressure (SBP)	Mean (SD)			ANOVA	
	Group 1(n=20)	Group 2(n=20)	Group 3 (n=10)	F-value	p-value
Base	58.65 (3.27)	61.55 (5.40)	60.60 (4.12)	2.23	0.12(NS)
2 week	54.30 (3.13)	55.80 (3.04)	61.00 (4.03)	14.16	<0.001*
4 week	57.40 (2.26)	58.70 (2.62)	59.40 (3.78)	2.08	0.14(NS)
6 week	58.10 (2.00)	60.00 (3.24)	58.80 (3.55)	2.21	0.12(NS)
8 week	58.40 (2.56)	60.40 (3.22)	58.60 (2.84)	2.69	0.08(NS)
4 month	57.90 (2.47)	60.10 (3.34)	58.40 (3.37)	2.80	0.07(NS)
6 month	58.00 (2.43)	60.10 (3.34)	58.40 (3.37)	2.62	0.08(NS)
F value(df1,df2)[#]	15.24(2.35,44.72)	48.99(1.78, 33.82)	7.80(2.58, 23.23)		
p-value	<0.001*	<0.001*	0.001*		

[#]Repeated Measures ANOVA

Table 5: Comparison of Glucose between the study groups at different time interval

Glucose	Mean (SD)			ANOVA	
	Group 1(n=20)	Group 2(n=20)	Group 3 (n=10)	F-value	p-value
Base	83.85 (2.78)	79.20 (5.91)	76.50 (2.99)	11.04	<0.001*
2 week	78.10 (4.67)	74.70 (4.56)	76.50 (2.59)	3.13	0.05(NS)
4 week	81.50 (4.58)	76.85 (4.16)	75.70 (2.87)	9.17	<0.001*
6 week	81.25 (5.19)	77.40 (4.24)	74.80 (2.90)	7.90	0.001*
8 week	80.45 (3.99)	76.80 (3.14)	75.30 (3.23)	8.92	0.001*
4 month	79.95 (3.90)	76.25 (2.53)	75.10 (2.81)	10.19	<0.001*
6 month	80.40 (4.31)	77.00 (2.79)	74.40 (3.20)	10.44	<0.001*
F value(df1, df2)[#]	10.62(2.93, 55.61)	9.83(2.55,48.39)	11.14(2.77, 24.88)		
p-value	<0.001*	<0.001*	<0.001*		

[#]Repeated Measures ANOVA

Table 6: Color change of the hemangiomas

		Group			Total	p-value
		1	2	3		
Base	Bluish	5(25.0%)	13(65.0%)	4(40.0%)	22(44.0%)	0.04*
	Reddish	10(50.0%)	4(20.0%)	6(60.0%)	20(40.0%)	
	Reddish blue	5(25.0%)	3(15.0%)	(0.0%	8(16.0%)	
2 week	Bluish	3(15.0%)	(0.0%)	3(30.0%)	6(12.0%)	0.03*
	Reddish	10(50.0%)	7(35.0%)	6(60.0%)	23(46.0%)	
	Reddish blue	7(35.0%)	12(60.0%)	1(10.0%)	20(40.0%)	
	Light red	(0.0%	1(5.0%)	0.0%	1(2.0%)	
4week	Bluish	0	0	3(30.0%)	3(6.0%)	0.006*
	Reddish	11(55.0%)	11(55.0%)	7(70.0%	29(58.0%)	
	Reddish blue	6(30.0%)	2(10.0%)	(0.0%	8(16.0%)	
	Light red	3(15.0%)	7(35.0%)	0.0%	10(20.0%)	
6week	Bluish	0	0	2(20.0%)	2(4.0%)	<0.001*
	Reddish	8(40.0%)	3(15.0%)	7(70.0%)	18(36.0%)	
	Reddish blue	5(25.0%)	1(5.0%)	1(10.0%)	7(14.0%)	
	Light red	7(35.0%)	16(80.0%)	0.0%	23(46.0%)	
8 week	Bluish	0	0	2(20.0%)	2(4.0%)	<0.001*
	Reddish	8(40.0%)	0	6(60.0%)	14(28.0%)	
	Reddish blue	3(15.0%)	0	1(10.0%)	4(8.0%)	
	Light red	9(45.0%)	20(100.0%)	1(10.0%)	30(60.0%)	
4 month	Reddish	5(25.0%)	0.0%	2(20.0%)	7(14.0%)	<0.001*
	Reddish blue	1(5.0%)	0.0%	3(30.0%)	4(8.0%)	
	Light red	14(70.0%)	10(50.0%)	5(50.0%)	29(58.0%)	
	Mild discoloration	0.0%	10(50.0%)	(0.0%	10(20.0%)	
6 month	Reddish	3(15.0%)	0.0%	2(20.0%)	5(10.0%)	<0.001*
	Reddish blue	0	0	3(30.0%)	3(6.0%)	
	Light red	17(85.0%)	7(35.0%)	5(50.0%)	29(58.0%)	
	Mild discoloration	0.0%	13(65.0%)	0.0%	13(26.0%)	

Fisher's exact test

In the present study (as seen in table 6), it was observed that there was a significant color change in the lesion in each group. After 6 months of study period, in Group 1, 85% children, color reduced to light red color and 0% reached to mild discoloration whereas in Group 2, 65% children, lesion just had mild discoloration and 35% had light red color. In Group 3, 58% children, color reduced to light red color and 26% just had mild discoloration. So it was observed that there was maximum color change towards normal in Group 2.

DISCUSSION

Infantile hemangioma is the most common benign infantile soft tissue tumor occurring in 5-10% children less than 1 year of age. There is an increased predominance in females with a ratio of 3-5:1, as observed in previous study by Mulliken and Fishman et al. [9] Similar observation was also made in our study with female to male ratio of 2.8:1. Infantile hemangiomas commonly occur as a single cutaneous lesion seen in 80% of the cases over head and neck region as observed in previous study done by Iwata et al. [10] In the present study, 86% of the cases were single cutaneous lesions mainly involving head and neck region. Majority (68%) of cases had oval shape which was not observed in any previous studies.

In the previous studies by Jackson [11] in 1998 and Mullikenet al [9] in 2000, it

was observed that there was spontaneous complete regression of the lesion in 50% of the cases up to 5 years of age, 70% up to 7 years of age and gradual regression till 10-12 years in color and bulk of the lesion. In our study, group 3 (which is control group) showed 10% and 12.6% mean reduction in the length and width of the lesion respectively in the 6 months of the study period. In 58% of children, color changed to light red and 26% children just had mild discoloration.

In the present study, no major side-effects and impact of the medications were noticed except for the changes in the systolic and diastolic blood pressure, pulse rate and blood glucose levels which were statistically significant but clinically the variation was not significant. These results are again in good agreement with those of the study of Dr. Izadpanah, [5] who reviewed the reports published from 1946 to 2012 and showed 18% patients had side-effects who were receiving prednisolone and 14% patients receiving Propranolol.

Study done by Malik et al [12] in 2013 showed a mean lesion reduction by 36% in patient receiving Propranolol alone and 32% in patients receiving the combination of Propranolol and prednisolone by 3months. In our study, it was observed that there was a mean length and width reduction in patients receiving combination of both medications (group 1) was 42.9% and 38.2% respectively by 6 months. In group 2 (receiving only Propranolol), there was mean length and width reduction of 69.5% and 72.4% respectively. It was observed that the length and width of the lesions were significantly varying in each time interval in group 1 and group 2.

In our study, there was a significant color change of the lesion in each group. After 6 months of study period, in 85% children color reduced to light red color and none of them reached to mild discoloration in group 1, whereas in group 2, 65% children lesion just had mild discoloration and 35% had light red color. It was also observed that there was maximum color change towards normal in group 2 receiving only Propranolol.

There were few limitations to this study, that it was a small patient population. Pro-angiogenic factors, especially (VEGF and b-FGF) couldn't be analyzed to detect the mechanism of action due to increased cost. There was lack of long term follow-up. Due to lack of follow-up, IH relapse rate after stopping medications couldn't be assessed after that study period.

CONCLUSION

Based on the result of this study, Propranolol is a safe, superior and more effective in treating IH compared to the traditional first-line oral corticosteroid treatment. We can avoid the unnecessary serious adverse-effects of the steroids in small children, where Propranolol is well tolerated and cost-effective with minimal or no major side-effects. So we propose that Propranolol alone should be considered as a first-line medication for the treatment of hemangiomas.

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