

Comparison of Efficacy between Propranolol and Steroid for Infantile Hemangioma

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ABSTRACT

Objective: To determine the efficacy and safety of propranolol compared with steroid as a first-line treatment for Infantile Hemangioma.

Study Design: A Randomized Control Trial study.

Place and Duration of Study: This study was conducted at the Department of Peads Surgery, Children Hospital, Multan and Department of Peads Surgery, NMU, Multan April 2014 to April 2017.

Materials and Methods: After obtaining ethical permission from hospital ethical committee and informed consent from parents of participants. A total of 84 patients were included in trial through non probability consecutive sampling technique, and divided into two equal groups. After completion of information and data collection, analyses was done by using SPSS software, for continuous variables mean \pm SD like age, size of hemangioma, weight, BMI and surface area was calculated. Frequencies and percentages were calculated for categorical variables like gender, color of hemangioma. T test and chi square were used to check difference in both groups. P value less than or equal to 0.05 was considered as significant.

Results: Overall, 84 patients were included in this study, both genders. The study group was further divided into two equal groups, 50% (n=42) in each. Mean volume, surface area and height of lesion was smaller in steroid group but, the difference was statistically insignificant $p=0.801$, $p=0.479$ and $p=0.402$ respectively.

Conclusion: Results of our study revealed that therapeutically propranolol is not inferior to steroids in treatment of infantile hemangioma.

Key Words: Hemangioma, Propranolol, Steroids, Infants.

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INTRODUCTION

In infants and young adults infantile hemangioma is the leading type of tumor which is not problematic if in small size¹. Place of hemangioma and its associated complications like bowel obstruction, respiratory obstruction, and vision loss due to abnormal growth of eye require treatment modalities. In infants infantile hemangioma (IH) treated with steroids and found to be antiangiogenic in vitro setting. Steroids also found effective clinically but their long term use can cause some serious complications like growth problems and gastroesophageal reflux^{2,3}.

At the point where steroids does not affect an immune modulator or anti-cancer drug interferon Alfa can be used in cases of severe hemangioma⁴. Interferon Alfa itself have some serious adverse effects like high fever, systemic myalgia, and muscle pain if it is more severe

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liver problems, thyroid disease and neurological side effects may occur⁵. Because of these lot of complications pediatric patients does not accept treatment they prefer to live without treatment⁶.

Another new treatment was introduced in 2008 and improvement was observed when beta blocker propranolol was used. After this initial step many centers conducted studies and case reports on propranolol use for the treatment of IH^{7,8}. Propranolol used worldwide in treatment of IH but data available on this topic and it's off label use is insufficient. Its efficacy and safety also compared with steroids⁹. Another trial was conducted in 2015 but results of this study do not suggested propranolol as drug of choice and 1st line treatment. Multiple studies and comparative trials required to label propranolol¹⁰. In this study we compared steroids with propranolol to check the efficacy and safety of propranolol over steroid use in treatment of IH.

MATERIALS AND METHODS

This randomized control trial was conducted in Department of Peads Surgery, Children Hospital, Multan and Department of Peads Surgery, NMU, Multan April 2014 to April 2017. After obtaining ethical permission from hospital ethical committee and informed consent from parents of participants. Total

number 60 patients included in the study and divided into two equal groups (group C and P) by lottery method in which every patient has equal chances to be included in the group. Children from birth to 9 months age who were diagnosed with IH, normal cardiac function and not treated for IH were included in the study. Children of preterm delivery, any congenital anomaly and co morbid disease were excluded from the study. Size of tumor was measured with magnetic resonance imaging (MRI).

In group P patients were given propranolol 3 mg/kg per day orally three times in a day and patients were admitted in hospital and dose reached to maximum doses on their fix timing. After one hour start of medication regular monitoring was started for heart rate, hypoglycemia, and blood pressure and breathing status. After three days patient was discharged and asked for follow up four hourly till 20 weeks from the day of initial treatment. Doses were adjusted; study protocol was not followed at the point where guardians requested for further treatment of remaining IH. Treatment was reevaluated if any complications were observed.

Group C treated by giving steroid prednisolon 1 mg/ml syrup oral at dose of 2 mg per kg. Primary outcome of this study is clinical response of medicine after sixteen weeks; it was labeled as regression. About 25% decrease in volume, surface area and height in hemangioma labeled as regression. Secondary variables include surface area of hemangioma, volume and height of hemangioma. After completion of information and data collection material entered into SPSS software and analyzed for continuous variables (mean \pm SD) like age, size of hemangioma, weight, BMI and surface area, categorical variables (number and percentages) like gender, color of hemangioma. Independent sample t-test and chi-square test was applied to see significance. P value less than or equal to 0.05 was considered as significant.

RESULTS

Overall, 100% (n=84) patients were included in this study, both genders. The study group was further divided into two equal groups, 50% (n=42) in each. Gender distribution, in propranolol group, was observed as 59.5% (n=25) males and 40.5% (n=17) females. While, in steroid group, there were 57.1% (n=24) males and 42.9% (n=18) females. The mean age, weight, height, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and body temperature of the propranolol group patients was 3.28 \pm 2.19 years, 5.64 \pm 2.63 kg, 61.47 \pm 1.71cm, 88.12 \pm 1.85 mm Hg, 49.76 \pm 1.80mm Hg, 129.80 \pm 1.72beats/min, 36.97 \pm 2.86 beats/min and 38.74 \pm 1.98 $^{\circ}$ C respectively. While, the mean age, weight, height, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate and body temperature of the propranolol group patients was

3.64 \pm 1.96 years, 6.04 \pm 2.34kg, 61.66 \pm 1.67 cm, 91.69 \pm 1.31 mm Hg, 51.92 \pm 1.77 mm Hg, 141.76 \pm 2.08 beats/min, 36.76 \pm 2.56beats/min and 38.24 \pm 2.11 $^{\circ}$ C respectively. For propranolol group, location of hemangiomas i.e. scalp, face, chest, abdomen, back, upper extremity and lower extremity noted as 7.1% (n=3), 59.5% (n=25), 16.7% (n=7), 4.8% (n=2), 7.1% (n=3), 14.3% (n=6) and 7.1% (n=3) respectively.

Table No. 1: Demographic characteristics of the study groups

Characteristics	Propranolol Group(n=42)	Steroid Group (n=42)	Test of Sig.
Gender	M=59.5% (n=25), F=40.5% (n=17)	M=57.1% (n=24), F=42.9% (n=18)	χ^2 =0.049, p=0.825
Age (years)	3.28 \pm 2.19	3.64 \pm 1.96	t=-0.78, p=0.433
Weight (kg)	5.64 \pm 2.63	6.04 \pm 2.34	t=-0.744, p=0.459
Height (cm)	61.47 \pm 1.71	61.66 \pm 1.67	t=-0.52, p=0.608
Blood pressure Systolic (mm Hg)	88.12 \pm 1.85	91.69 \pm 1.31	t=-10.11, p=0.000
Blood pressure Diastolic (mm Hg)	49.76 \pm 1.80	51.92 \pm 1.77	t=-5.55, p=0.000
Heart rate (beats/min)	129.80 \pm 1.72	141.76 \pm 2.08	t=-28.63, p=0.000
Respiration rate (beats/min)	36.97 \pm 2.86	36.76 \pm 2.56	t=0.361, p=0.719
Body temperature ($^{\circ}$ C)	38.74 \pm 1.98	38.24 \pm 2.11	t=1.12, p=0.265
Hemangiomas			
Location			
Scalp	7.1% (n=3)	11.9% (n=5)	χ^2 =0.55, p=0.457
Face	59.5% (n=25)	73.8% (n=31)	χ^2 =1.93, p=0.165
Chest	16.7% (n=7)	4.8% (n=2)	χ^2 =3.11, p=0.078
Abdomen	4.8% (n=2)	7.1% (n=3)	χ^2 =0.213, p=0.645
Back	7.1% (n=3)	11.9% (n=5)	χ^2 =0.553, p=0.457
Upper extremity	14.3% (n=6)	16.7% (n=7)	χ^2 =0.09, p=0.763
Lower extremity	7.1% (n=3)	11.9% (n=5)	χ^2 =0.553, p=0.457
Color			
Red	66.7% (n=28)	92.9% (n=39)	χ^2 =8.93, p=0.003
Purple	16.7% (n=7)	4.8% (n=2)	χ^2 =3.11, p=0.078

P<0.05 is considered as significant

While, location of hemangiomas of steroid group i.e. scalp, face, chest, abdomen, back, upper extremity and

lower extremity noted as 11.9% (n=5), 73.8% (n=31), 4.8% (n=2), 7.1% (n=3), 11.9% (n=5), 16.7% (n=7) and 11.9% (n=5) respectively. Color, for propranolol group, red and purple observed as 66.7% (n=28) and 16.7% (n=7) respectively. Whereas; color, red and purple observed as 92.9% (n=39) and 4.8% (n=2) respectively, for steroid group. The differences between demographic characteristics were statistically insignificant except systolic blood pressure, diastolic blood pressure, heart rate and red color. (Table. 1).

Table No. 2: Outcome Variables

Characteristics	Propranolol Group (n=42)	Steroid Group (n=42)	Test of Sig.
Size			
Baseline Volume, mm ³ by MRI*	29672.70 ±25.17	29682.8 ± 24.31	t=0.25, p=0.801
Volume, mm ³ by MRI*	14129 ± 11.98	14345 ± 13.07	
Regression in Baseline Volume, mm ³ by MRI*	15543.7	15337.8	
Baseline Surface area, mm ²	4099.01 ± 49.72	4145.34 ± 44.19	t=0.71, p=0.479
Surface area, mm ²	1322.26 ± 16.03	1375.23 ± 14.25	
Regression in baseline Surface area, mm ²	2776.75	2770.11	
Baseline Height, mm	8.40 ± 3.12	9.87 ± 2.55	t=0.84, p=0.402
Height, mm	4.66 ± 1.74	5.65 ± 1.60	
Regression in baseline Height, mm	3.74	4.22	

* MRI, magnetic resonance imaging, P<0.05 is considered as significant

The main outcome variables of this study were volume, surface area and height. The MRI scans were conducted for all the patients, the IH baseline volume was 29672.70 ± 25.17 mm³ for the propranolol group and it was 29534.2 ± 24.31 mm³ for the steroid group. The MRI scans were conducted for all the patients, the IH volume was 14129 ± 11.98 mm³ for the propranolol group and it was 14345 ± 13.07 mm³ for the steroid group. Regression in baseline volume, mm³ by MRI, for propranolol and Steroid was 15543.7 and 15337.8 respectively. But, the difference was statistically insignificant (p=0.801). An image of the lesion was taken for all participants in each group, and the mean baseline surface area for the propranolol group was 4099.01 ± 49.72 mm², while it was, for the steroid group, 4145.34 ± 44.19 mm². The mean surface area for the propranolol group was 1322.26 ± 16.03 mm², while it was, for the steroid group, 1375.23 ± 14.25 mm². Regression in baseline surface area, mm² for propranolol and Steroid was 2776.75 and 2770.11 respectively. The difference was statistically insignificant (p=0.479). The baseline height, for the

propranolol and steroid group, was 8.40 ± 3.12 mm and 9.87 ± 2.55 mm respectively. The height, for the propranolol and steroid group, was 4.66 ± 1.74 mm and 5.65 ± 1.60 mm respectively. Regression in baseline height, mm for propranolol and Steroid was 3.74 and 4.22 respectively. The difference was statistically insignificant (p=0.402). (Table. 2).

DISCUSSION

Since the day of propranolol introduced it was globally accepted for treatment of hemangioma in infants because it is found to be effective as steroids. But there was limited literature available on effectiveness and its efficacy over steroids. In our study we found more reduced volume, surface area and height with steroids as compare to propranolol but values are not significant (p=0.801, p=0.479, p=0.402).

A recent study was conducted by Malik MA et al¹¹ on comparison of prednisolone and propranolol and reported that propranolol have better therapeutic effects with safety and efficacy, combination of both prednisolone and propranolol is also effective but less than propranolol alone, steroid alone have some serious adverse effect due to which its non compliance is too much. This study is comparable with our study.

Another recent study was conducted by Bauman NM et al¹² in 2014 and concluded that both drugs are equally beneficial; steroids have rapid effect and treatment option. On other hand propranolol has safety better than steroids as it has little complication rate and better compliance rate as compare to steroids. This study is also comparable with our study. Another study conducted by Léauté-Labrèze C et al¹³ and concluded that propranolol is an effective drug for the treatment of infantile hemangioma as other drugs like steroids.

Bennett ML et al¹⁴ also conducted a similar study on use of propranolol and steroids in treatment of hemangioma and reported that systemic steroids are better and more effective in subcutaneous hemangioma. He use similar variables in his study as we use in our trial. Similar studies were conducted by Price CJ et al¹⁵, Enjolras O et al¹⁶, they used same variables and reported that propranolol is as effective as steroids in treatment of hemangioma.

In our study systolic blood pressure, diastolic blood pressure, heart rate and red color of hemangioma are statistically significant shows that propranolol is not bad for hemodynamic stability. In a study Izadpanah A et al¹⁷ reported that propranolol is a favorite drugs as compared to corticosteroids when use in treatment of IH in infants. Its adverse effects profile is more safe and reliable as compared to drugs of corticosteroids group. This study is also comparable with our findings.

Propranolol have some major side effects like bradycardia, hypotension and hypoglycemia, to overcome these complications some studies suggested selective beta blocker (Atenolol) in place of propranolol

with more safety and superiority^{18, 19}. In a study Chim H et al²⁰ recommended propranolol 3 mg/kg or 1 mg/kg is more effective in treatment of hemangioma of infancy

CONCLUSION

Results of our study revealed that therapeutically propranolol is not inferior to steroids in treatment of infantile hemangioma.

Author's Contribution:

Concept & Design of Study: Muhammad Kashif
 Drafting: Muhammad Kashif, Abdus Sami
 Data Analysis: Abdus Sami, Neelam Mumtaz
 Revisiting Critically: Muhammad Kashif, Abdus Sami, Neelam Mumtaz
 Final Approval of version: Muhammad Kashif

Conflict of Interest: The study has no conflict of interest to declare by any author.

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