ORIGINAL ARTICLE

The Outcome of Combination of Low Dose Oral Prednisolone and Oral Propranolol for the Treatment of Infantile Hemangioma

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ABSTRACT
Objective: To determine the outcome of combination of low dose oral Prednisolone with oral propranolol for the treatment of infantile hemangioma.
Study Design: Experimental Study
Setting: Department of Neonatal & Pediatric Surgery, Plastic Surgery, Dermatology and Ophthalmology, Bahawal Victoria Hospital, Bahawalpur.
Duration of Study: 7th January 2013 to 6th July 2013.
Subjects and Methods: Seventy three cases fulfilling inclusion criteria were registered through Outpatient Departments of Neonatal & Pediatric surgery, plastic surgery, Dermatology and Ophthalmology, Bahawal Victoria Hospital, Bahawalpur. Diagnosis were confirmed by consultant pediatric Surgeon (assistant professor and above having 5 years experience) clinically and by Color Doppler ultrasonography (clustered dilated, tortuous blood vessels with Sluggish blood flow) by consultant radiologist (assistant professor and above having 5 years experience). Demographic history including age (in years) and sex (male or female) were taken. Approval from the hospital ethical committee was taken. Written informed consent was taken from the parents/guardians of the patients after discussing the risks and benefits of the drugs.
All the patients received treatment with oral prednisolone in a dose of 1mg/kg/day and propranolol in a dose of 0.5 mg/kg/day twice a day (BID) and increase up to 1.5mg/kg/day BID within three days with close monitoring of heart rate, blood pressure and blood glucose as an inpatient. Treatment was given for 3 months to all patients then titer down for two weeks before cessation of treatment. In case of early response i.e, before 3 month, drugs were titer down for two weeks before cessation.
The follow up of the patients were performed at 7th day after initiation of treatment, then 1st month and finally at 3rd month. Heart rate, blood pressure, random blood sugar and treatment compliance was checked during each visit along with outcome parameter i.e. response which was categorized as excellent, good, moderate, slight improvement or no effect taking good to excellent response as acceptable outcome by measuring the size of IHs in terms of maximum dimensions in millimeters by using 100 mm horizontal scale on photograph taking by using 12 mega pixel digital camera. All the information was collected on a specially designed proforma (attached).
Results: In this study, 36.99%(n=27) had 1 year of age, 32.88%(n=24) had 2 years and 30.13%(n=22) had 3 years of age, mean+SD: 1.96+0.54 years, 53.42%(n=39) were male and 46.58%(n=34) were females, frequency of response of the treatment was recorded as 56.16%(n=41) had excellent, 23.29%(n=17) had good, 15.07%(n=11) had moderate response, 4.11%(n=3) had slight improvement and 1.37%(n=1) had no effect while frequency of acceptable outcome revealed as acceptable in 79.45%(n=58) while 20.55%(n=15) had not acceptable outcome.
Conclusion: This study concludes that the combination of low dose oral propranolol with that of oral Prednisolone for the treatment of infantile hemangioma is effective and safe

Key Words: Infantile hemangioma, management, combination of low dose oral prednisone with oral propranolol, effectiveness.

INTRODUCTION

Infantile hemangiomas (IHs) are the most common vascular tumours of infancy, occurring in 5% to 10% of infants[1]. Mostly infantile hemangiomas are small, but they can be large, disfiguring lesions with serious complications. Hemangiomas might also involve the orbit, airway, or visceral organs, such as the liver, brain intestinal tract, or lungs[2]. They generally become evident within first few days of life and are characterized by an initial phase of rapid endothelial cell proliferation during the first year of life followed by a phase of slow involution[3].

Size and location of IHs are factors predicting possible complications like ulceration (hemangiomas located over friction areas like lip and perineum), functional impairment (hemangiomas located around orificial areas like eyes and nostril and disfigurement due to residual scarring (large facial hemangiomas)[4].

Until recently, the mainstay of treatment of IHs has been corticosteroids in various forms, including topical, intralesional, and oral formulations, with the most common being oral prednisolone. A meta-analysis[5] reviewed 24 case series of infants who were treated with systemic steroids. The patients received a mean dose of 2.9 mg/kg of prednisone daily for an average of 1.8 months. The response rate was found to be 84%, with the greatest response occurring in children treated in the early proliferative phase of the lesion[6]. The standard treatment regimen is 2 to 4 mg/kg of oral prednisone or prednisolone daily[2]. Other treatment modalities for complicated IH include interferon alfa-2a, imiquimod, vincristine, cyclophosphamide, pulsed-dye laser, and most recently, propranolol[5,6].

Propranolol is a nonselective beta-blocker that has been in use for around 4 decades by cardiologists, endocrinologists, pediatricians, and psychiatrists. Its safety profile is well established when given to appropriate patients[7,8]. Propranolol has been associated with adverse events such as bradycardia, hypotension, hypoglycemia and bronchospasm[9,10].

Ninety seven percent (97%) of patients showed improvement in the quality of their treated infantile hemangiomas with propranolol therapy where 60% of the patients showed a final excellent response with more than 75% reduction in the size of the lesion (P<0.001), 20% showed a good response with more than 50% decrease in size of the IH, 16.6% showed a moderate response with less than 50% reduction in size and only one patient 3.3% showed no response to treatment[11].

Oral prednisolone and propranolol have shown excellent results individually for the treatment of problematic IH. However, the combination of the two drugs in lower doses may also be used for the treatment of IH to avoid the complications associated with high doses of both drugs. One such study showed 95% results when treated with prednisolone and propranolol in combination[12].

This mode of treatment for infantile hemangiomas is very safe and cost effective. The studies in this regard are lacking, few studies are available internationally, but no national/local study available. Therefore, this will help us making local policies for patients and help in reducing the morbidity.

MATERIAL AND METHODS

Study was Descriptive case series. Research was conducted at Department of Neonatal & Pediatric Surgery, Plastic Surgery, Dermatology and Ophthalmology, Bahawal Victoria Hospital, Bahawalpur. The calculated Sample size was 73 cases with 5 % margin of error, 95% confidence level taking expected percentage of response 95%. The sampling technique was Consecutive (Non-probability) sampling. Patients with age ranges of 0-3 years; both males and females; all patients having infantile haemangiomas over body surface and size more than 10mm were included in the study while patients having known cardiac problems, bronchial asthma, previously treated either medically or surgically; patients with lack of consent and incomplete follow up; infantile hemangiomas involving internal organs/body cavities and those who needed urgent treatment due to impingement on vital structures were excluded from the study.

Seventy three cases fulfilling inclusion criteria were registered through Outpatient Departments of Neonatal & Pediatric surgery, plastic surgery, Dermatology and Ophthalmology, Bahawal Victoria Hospital, Bahawalpur. Diagnosis were confirmed by consultant pediatric Surgeon (assistant professor and above having 5 years experience) clinically and by Color Doppler ultrasonography (clustered dilated, tortuous blood vessels with Sluggish blood flow) by consultant radiologist (assistant professor and above having 5 years experience). Demographic history including age (in years) and sex (male or female) were taken. Approval from the hospital ethical committee was

taken. Written informed consent was taken from the parents/guardians of the patients after discussing the risks and benefits of the drugs.

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The follow up of the patients were performed at 7th day after initiation of treatment, then 1st month and finally at 3rd month. Heart rate, blood pressure, random blood sugar and treatment compliance was checked during each visit along with outcome parameter i.e. response which was categorized as excellent, good, moderate, slight improvement or no effect taking good to excellent response as acceptable outcome by measuring the size of IHs in terms of maximum dimensions in millimeters by using 100 mm horizontal scale on photograph taking by using 12 mega pixel digital camera. All the information was collected on a specially designed proforma.

All the collected data was entered into SPSS version 10 and analyzed. The qualitative data like demographics (sex; male or female), response (excellent, good, moderate, slight improvement or no effect and acceptable outcome was described as frequency distribution.

Quantitative data like age (in years) and size of IH (in millimeters) was presented as means and standard deviations. The stratification was done for effect modifiers i.e., age, sex, and type of hemangioma. Post stratification Chi-square test was applied. P<0.05 was taken as significant.

RESULTS

A total of 73 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the outcome of combination of low dose oral Prednisolone with oral propranolol for the treatment of infantile hemangioma.

Age range was from 0-3 years with mean age of 1.96+0.54 years. Majority of patients were <1 year i.e. 27 (36.99%) as shown in Table 1. Male patients were 39 (53.42%) and female were 34 (46.72%) with male to female ration of 1:1.15 as shown in Table 2.

Mean Size of IH was 22.39 ± 6.71 mm with majority of patients between 15-35 mm i.e. 62 (84.93%) as shown in Table 3.

Table No. 1: Age Distribution; (n=73)

Age(in years)	No. of patients	%
0-1	27	36.99
>1-2	24	32.88
>2-3	22	30.13
Total	73	100

Mean+SD: 1.96+0.54

Table No. 2: Gender Distribution; (n=73)

Gender	No. of patients	%
Male	39	53.42
Female	34	46.58
Total	73	100

Table No. 3: Size Of IH; (n=73)

Size of IH	No. of patients	%
15-35 mm	62	84.93
>35 mm	11	15.07
Total	73	100

Mean ± SD = 22.39 ± 6.71

Table No. 4: Frequency Of Response Of The Treatment; (n=73)

Response	No. of patients	%
Excellent	41	56.16
Good	17	23.29
Moderate	11	15.07
Slight improvement	3	4.11
No effect	1	1.37
Total	73	100

Table No. 5: Frequency Of Acceptable Outcome; (n=73)

Acceptable outcome	No. of patients	%
Yes	58	79.45
No	15	20.55
Total	73	100

Frequency of response of the treatment was recorded as 56.16%(n=41) had excellent, 23.29%(n=17) had good, 15.07%(n=11) had moderate response, 4.11%(n=3) had slight improvement and 1.37%(n=1) had no effect. (Table No. 4)

Frequency of acceptable outcome revealed as acceptable in 79.45% (n=58) while 20.55% (n=15) had not acceptable outcome. (Table No. 5)

Stratification for frequency of acceptable outcome with regards to age was shown in Table No. 6.

Stratification for frequency of acceptable outcome with regards to gender was shown in Table No. 7.

Stratification for frequency of acceptable outcome with regards to type of hemangioma was shown in Table No. 8.

Table No. 6: Stratification For Frequency Of Acceptable Outcome With Regards To Age; (n=73)

Age(in years)	Acceptable Outcome		p-value
	yes	no	
0-1	21 (77.78%)	06 (22.22%)	0.940
>1-2	19 (79.17%)	05 (20.83%)	
>2-3	18 (81.82%)	04 (18.18%)	
Total	58 (79.45%)	15 (20.55%)	

Table No. 7: Stratification For Frequency Of Acceptable Outcome With Regards To Gender; (n=73)

Gender	Acceptable Outcome		P value
	yes	no	
Male	30 (76.92%)	09 (23.08%)	0.567
Female	28 (82.35%)	06 (117.65%)	
Total	58 (79.45%)	15 (20.55%)	

Table No. 8: Stratification For Frequency Of Acceptable Outcome With Regards Type Of Hemangioma; (n=73)

Type of Hemangioma	Acceptable Outcome		P value
	yes	no	
Localized	56 (96.55%)	2 (3.45%)	0.000
Segmental	2 (13.33%)	13 (86.67%)	

DISCUSSION

Infantile hemangiomas (IH) are the most common infantile tumor, with a frequency of 4-10%[13]. Recently, there has been an interest in propranolol and other beta-blockers in the treatment of IH. Propranolol may be more effective and safer than previously established therapies, and may be an alternative when more widely accepted treatments for IH have failed. Initial studies suggest that it may also be used as a first-line therapy.

A previous study,[14] compared the clinical effectiveness of oral propranolol with that of oral prednisone in the treatment of infantile hemangiomas (IH) and concluded that Propranolol appears superior to oral prednisone in inducing more-rapid and greater clinical improvement in this study.

Oral prednisolone and propranolol have shown excellent results individually for the treatment of problematic IH. However, the combination of the two drugs in lower doses may also be used for the treatment of IH to avoid the complications associated with high doses of both drugs. One such study showed 95% results when treated with prednisolone and propranolol in combination[12].

This mode of treatment for infantile hemangiomas is very safe and cost effective. The studies in this regard are lacking, few studies are available internationally, but no national study is available. Therefore, the results of the study may help us by making local policies for patients and help in reducing the morbidity.

In this study, 36.99%(n=27) had 1 year of age, 32.88%(n=24) had 2 years and 30.13%(n=22) had 3 years of age, mean+SD: 1.96+0.54 years, 53.42%(n=39) were male and 46.58%(n=34) were females, frequency of response of the treatment was recorded as 56.16%(n=41) had excellent, 23.29%(n=17) had good, 15.07%(n=11) had moderate response, 4.11%(n=3) had slight improvement and 1.37%(n=1) had no effect while frequency of acceptable outcome revealed as acceptable in 79.45%(n=58) while 20.55%(n=15) had not acceptable outcome.

The findings of the study are in agreement with Buckmiller LM recorded that ninety seven percent (97%) of patients showed improvement in the quality of their treated in hemangiomas with propranolol therapy where 60% of the patients showed a final excellent response with more than 75% reduction in the size of the lesion (P<0.001), 20% showed a good response with more than 50% decrease in size of the IH, 16.6% showed a moderate response with less than 50% reduction in size and only one patient 3.3% showed no response to treatment[11].

Another study by Koaya ACA showed 95% results when treated with prednisolone and propranolol in combination[12].

Some-other trials may be done to confirm these findings, as very few studies are available nationally/internationally and these results may be considered as primary.

CONCLUSION

We concluded that the frequency of acceptable outcome of combination of low dose oral Prednisolone with oral propranolol for the treatment of infantile hemangioma is higher but more studies are required to authenticate these findings as no local study is available for comparison

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