ORIGINAL ARTICLE

Use of oral prednisolone with or without propranolol in the management of infantile hemangioma: A critical appraisal

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ABSTRACT

Introduction: Various medications have been tried to induce regression in hemangioma. We tried to find out the benefits of oral prednisolone versus propranolol in these lesions.

Objectives: The objective of this study was to assess the effect of oral prednisolone and propranolol in infantile hemangioma (IH) and also to compare their efficacy.

Materials and Methods: This was a prospective study from January 2008 to December 2012. Patients of hemangioma in high risk location with dimension >5 cm and/or area >20 cm^2 were included. Patients were randomized into Group A receiving oral prednisolone 5 mg/kg/day in tapering doses, Group B receiving oral propranolol 3 mg/kg/day and Group C receiving both. Patients were evaluated for response and $P < 0.05$ was considered to be significant.

Results: A total of 69 cases were included. Patients in each group were 24, 22 and 23 respectively. Mean age at presentation was 32 weeks (range 6-48 weeks). Therapy was initiated at 30.1 ± 9.2 weeks for 14.9 ± 2.1 weeks. Average tumor size at initiation was 28.2 ± 5.6 cm^2 in Group A, 24.9 ± 2.2 cm^2 in B and 22.7 ± 2.1 cm^2 in C. There was a significant response to treatment in Group A ($P = 0.04$) and insignificant in B ($P = 0.07$) and C ($P = 0.06$).

Conclusions: Oral prednisolone is a viable treatment option in the management of high risk IH and there is no added benefit of using propranolol either alone or in combination in the treatment of these cases. A large randomized controlled trial is needed to further validate this observation.

Key words: Infantile hemangioma, prednisolone, propranolol, response

INTRODUCTION

Presence of a bright red mass, that too in locations of obvious visibility in infants is horrifying and a source of concern to parents. It has long been advised to plan a conservative management and counsel the attendants in various literatures owing to the spontaneous regression in these cases. There are however certain definite indications demanding therapy in these cases. Various medications have been tried to induce regression in these lesions and oral prednisolone is what which has stood the test of time. Recent literatures support the use of propranolol in these cases, but the long-term results are awaited. We tried to find out the benefit of either agent in the management of these lesions and are compiling our results.

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AIMS AND OBJECTIVES

The objective of this study was to assess the effect of oral prednisolone and propranolol in regression of infantile hemangioma (IH) and to compare their efficacy.

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MATERIALS AND METHODS

This was a prospective study from January 2008 to December 2012 and patients were studied after obtaining clearance from institute ethical committee. All cases of IH in high risk location with any dimension more than 5 cm and/or area more than 20 cm^2 were included in the study. Patients whose parents did not give consent for the study, follow-up less than 3 months, poor patient compliance, any form of previous surgical intervention or intervention during therapy, any form of complication leading to alteration/modification in the therapy protocol were excluded from the study. High risk locations were defined as lesions located in the face especially near eyes, nose occluding vision and breathing, lesions with ulcerations or impending ulcerations, lesions with a history of rapid proliferation.

Patients were randomized into three groups. Group A received oral prednisolone 5 mg/kg/day[1,2] as 100 day regimen in tapering doses given on alternate days (due to logistics) and tapered to half every 20th day. Group B received oral propranolol 3 mg/kg/day[3] for 100 days. Group C received oral prednisolone 5 mg/kg/day and propranolol 3 mg/kg/day simultaneously.

For area calculation, measurements were done in the largest dimension and in the direction perpendicular to that. Photographs were taken using standard positioning and lighting at each visit. Patients were evaluated at 15 days, 1 month, 2 months and 3 months respectively to see regression. Change in dimension, color and consistency were noted during each visit. Response was marked as the regression observed at the 3rd month visit.

Responses in the lesions were graded as no response (<25% regression), partial response (25-50% regression) and good response (>50% regression). Mere change in color and consistency without change in the dimension of the lesion was considered as a partial response.

Data were compiled and analysis was performed using STATA software version 11.0 (StataCorp LP, Texas, USA). The statistical tests applied were Chi-square test, Wilcoxon signed rank test. *P* value was calculated using fisher exact test owing to the small sample size and the value < 0.05 was considered to be statistically significant.

RESULTS

A total of 73 patients were enrolled in the study for the duration from January 2008 to December 2012. Out of them, four cases were excluded due to the exclusion criteria already mentioned. There were 48 males and 21 females in the study with a male to female ratio of 2.28:1. Total number of patients in each group was 24, 22 and 23 respectively. The sex wise distribution and the mean area of the lesions were as shown in Table 1.

Mean age of the cases at presentation was 32 weeks (range 6-48 weeks). Therapy was initiated at a mean age of 30.1 ± 9.2 weeks for 14.9 ± 2.1 weeks. Average tumor size at the initiation of treatment was 28.2 ± 5.6 cm^2 in Group A, 24.9 ± 2.2 cm^2 in Group B and 22.7 ± 2.1 cm^2 in Group C respectively. The sex wise response to the therapy was as shown in Table 2. There was no significant difference in the response rate with respect to sex in various groups [Table 2].

There was statistically significant response to treatment in the Group A (P = 0.04) [Figures 1 and 2]. This response was insignificant in Group B (P = 0.07) and C (P = 0.06) respectively [Table 3].

DISCUSSION

IH is a benign proliferative endothelial lesion. IH is the most common tumor of infancy and is

Table 1: Pattern of distribution of the lesion (*n*=69)

Groups/ response	Sex	No. of cases	Age of presentation (in weeks)	Area of lesion (in cm^2)	Duration of therapy (in weeks)
Group A	Male	16	29.1±9.2	28.4±5.6	14.6±2.2
	Female	8	31.5±8.3	28.2±5.4	13.9±2.0
Group B	Male	17	26.8±5.9	24.7±2.2	14.9±2.7
	Female	5	29.9±5.3	25.1±2.2	13.8±2.9
Group C	Male	15	26.4±4.9	22.4±2.1	14.4±2.0
	Female	8	30.1±6.2	23.0±2.2	15.1±1.9
Total		69	30.1±9.2	25.3±2.3	14.9±2.1

Table 2: Sex wise distribution of response following treatment in various groups (*n*=69)

Groups/ response	Sex	No response	Partial response	Good response	*P* values
Group A	Male	4	5	7	0.07
	Female	2	3	3	
Group B	Male	8	5	4	0.20
	Female	2	2	1	
Group C	Male	4	7	4	0.06
	Female	3	3	2	
Total		23	25	21	

Table 3: Response rates in various groups (*n*=69)

Response/ group	No response	Partial response	Good response	*P* value
Group A	6	8	10	0.04
Group B	10	7	5	0.07
Group C	7	10	6	0.06
Total	23	25	21	-

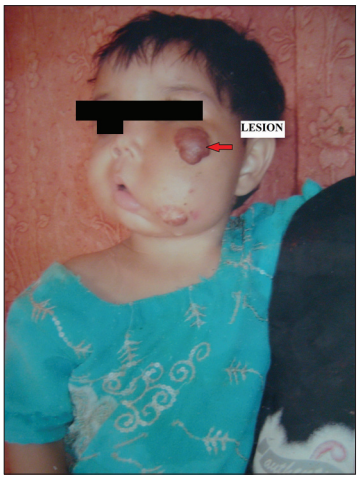

Figure 1: Lesion prior to therapy with prednisolone

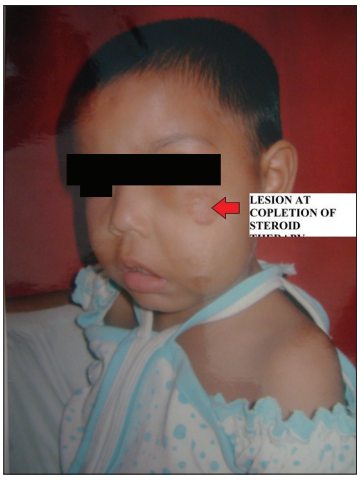

Figure 2: Lesion after prednisolone therapy

more commonly seen in girls and twins.[4,5] Usually observed male to female ratio is 1:3 world-wide while in India it is 1:2.[2] In our study, however, it was observed that the males were more as compared with females the reason for which is unexplained, this may probably be attributed to the importance given to a male child in our population. In most of the literature watchful waiting is what that is recommended for the management of IH. Therapy is indicated in lesions which are obstructing vision or the airway, damaging a critical structure (eyelid, lip and nose) and growing large enough to leave behind significant fibro fatty tissue or excess skin that would require operative intervention. For a small lesion, excision or intralesional steroid administration is recommended while for very large tumor therapy in the form of oral corticosteroids is recommended.[6] Oral corticosteroids have been the mainstay of therapy in growing IH, but dosage recommendations, duration of treatment, recommendations for monitoring during and after treatment and methods of tapering vary widely.[7,8] Various dosage schedules have been described for oral prednisolone, which ranges from 1 to 5 mg/kg/day either as daily or alternate day regimen.[1] In our study, we used oral prednisolone at the dose of 5 mg/kg/day on alternate day basis (i.e., 10 mg/kg/day on alternate days) due to logistic reasons. The dose was tapered at 20 days to half to complete the therapy in 100 days. Although, fairly high doses of corticosteroids are required for treating IH, our study and previous reports demonstrate that infants can tolerate this therapy remarkably well. Various and severe adverse effects have been reported with the oral corticosteroid use. Some of the effects are unusual and in most instances entirely reversible.[9,10] Poor growth has also previously been reported, but this was seen in none of our case, as the number of cases was small it is difficult to draw any conclusion. Oral prednisolone has been reported to be associated with a significant reduction in the progression of the IH in various previously published studies.[1,2,6] This was observed in our study also. Good response was seen in 10/24 cases, partial response in 8/24 and no response in 6/24. This difference was significant in these cases who were treated with steroids alone ($P = 0.04$).

Propranolol was serendipitously discovered to be effective in the treatment of IH in 2008. In the subsequent years, there has been increasing reports of its efficacy in IH and some concerns have been raised regarding potential toxicity. In addition, dosage recommendations have not been firmly established, ranging from lower doses (1-1.5 mg/kg/day) to higher doses, such as 3 mg/kg/day. Holmes *et al.*[11] reported a halt in progression in 100% of patients and significant regression in 87% of patients with IH treated at 3 mg/kg/day of propranolol. Studies with lower doses of propranolol have been reported to be efficacious. This therapy generally requires longer duration and is associated with a higher risk of rebound growth.[12,13] We used propranolol only in 22 cases. Good response was seen in 5/22 cases, partial response was seen in 7/22 and no response was seen in 10/22. The response observed in cases treated with propranolol alone was not significant ($P = 0.07$). None of the patient showed any complications during the therapy.

Combined use of oral prednisolone with propranolol has not been very popular. There are isolated case reports of the use of these two modalities simultaneously and the authors who have studied this claim complete regression with the combined use.[14,15] We used both the drugs in 23 cases. Good

response was seen in 6/23 cases, partial response was seen in 10/23 and no response was seen in 7/23. This observation was also insignificant ($P = 0.06$).

Thus, significant clinical response was seen in cases treated with prednisolone only. This response was insignificant in those treated with propranolol alone or in combination with steroids. This observation points toward the fact that still oral prednisolone alone is the gold standard in the management of IH. Though there have been reports of efficiency of propranolol in the management of hemangioma, we couldn't find any significant benefit of its use. The use of propranolol in the management of hemangioma needs further validation by a large randomized controlled trial.

CONCLUSIONS

Oral prednisolone is a viable and time tested treatment option in the management of high risk IH and there is no added benefit of using propranolol either alone or in combination in the treatment of these cases. A large randomized controlled trial is needed to further validate this observation.

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