

Management of Alarming Hemangiomas with Oral Prednisolone in Infants

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Abstract

Background: Treatment of hemangiomas remains a contentious and difficult issue for the physicians as well as for the surgeons. The numerous modality of treatment for hemangiomas testifies that no single mode of treatment is entirely satisfactory in their management. However, for alarming hemangiomas oral prednisolone had been used for long with encouraging results.

Methods: From a vast number of patients with hemangiomas attending the out-patient departments (OPDs) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka Shishu Hospital (DSH), Rajshahi Medical College Hospital (RMCH) and BIRDEM General Hospital between 1999 through 2014, we had selected consecutively 462 infants with alarming hemangiomas. The whole study population (462 infants with alarming hemangiomas) received oral prednisolone at a dose of 2-4 mg/kg/day, and the results were observed sequentially in serial follow-ups.

Results: About 71% patients showed substantial regression of the hemangiomas with oral prednisolone therapy after a mean duration of treatment of 6 months. Few adverse effects were associated with oral prednisolone but these were mostly transient and reversible.

Conclusion: The authors assert that the management of alarming hemangiomas with oral prednisolone therapy is safe and effective.

Key words: Alarming hemangioma, treatment modality, oral prednisolone

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Introduction

Hemangiomas represent the most common tumors of infancy with a documented incidence of 1.0 to 2.6%. Alarming or life-threatening hemangiomas, as suggested by Mulliken¹, include a group of hemangiomas that proliferate very rapidly to encroach or impinge upon some vital structures of the body as to cause impairment of body functions and health, or may even progress to endanger life. This group also includes hemangiomas

that have developed complications such as infection, ulceration or bleeding.

Hemangiomas typically exhibit unique biological behavior. They grow rapidly during the first year of life followed by a phase of slow regression. It is well accepted that most of the hemangiomas do regress spontaneously and need no active treatment²⁻⁴. But obviously a “wait and watch” policy may turn out to be harmful or detrimental for a patient with alarming hemangioma. And, definitely some modality of treatment must be instituted.

The use of corticosteroids in the management of hemangiomas started from the serendipitous discovery of regression in the size of hemangiomas while treating patients with Kasabach-Merritt syndrome having thrombocytopenia due to platelet trapping⁵. Since then scientists used corticosteroids in various forms and routes⁶⁻⁸. Intralesional steroids and systemic or oral prednisolone achieved remarkable and consistent

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results. In our study, we had used oral prednisolone in a dose of 2-4 mg/kg/day as an initial starting dose for 4-6 weeks and then reduced the dose to half and continued for 8-10 weeks. A maintenance dose had been used in some patients to achieve a complete involution. This study included a total of 462 consecutive infants with alarming hemangiomas. The patients who were lost to follow up were excluded from the study.

Methods

This quasi experimental study was designed based on the cross-section of patients who attended the OPDs of BSMMU, DSH, RMCH and BIRDEM General Hospital. The time period extended from March 1999 through May 2014. We had selected consecutively among the patients with hemangiomas those who fall in the group of alarming hemangiomas. A total of 2881 patients were recorded in the OPDs but only 497 were classified as alarming hemangiomas. Out of these patients, 35 were lost to follow up and the remaining 462 were included in this study.

The detailed history relating to the hemangioma was taken from the parents/caregivers. The size/volume of the hemangiomas, their color, site(s), number(s), situation (cutaneous/subcutaneous), time of appearance, rate of growth and presence of any complication were noted. Pre-treatment photographs were taken. The parents/caregivers were briefed regarding the nature of the disease and regarding the treatment to be instituted with its potential adverse effects. Treatment with oral prednisolone had been started after thorough counseling and after obtaining written consent for enrollment in the research from the parents/caregivers.

Initially, oral prednisolone was prescribed in a dose of 2-4 mg/kg/day in divided dose for 4-6 weeks. During the first follow-up, repeat general and systemic examinations of the patients was performed including the local examination of the hemangioma. The lesions were photographed again to note any change in color, size or appearance. This routine was followed in each follow-up. The dose of the oral prednisolone was halved in the first follow-up and continued for 8-10 weeks if the initial response was satisfactory. In the next follow-up, a maintenance dose - determined in respect to the treatment response and in the light of appearance of adverse effect- had been instituted for a further period of 8-10 weeks.

The response to treatment was assessed and evaluated in each follow-up. The reduction in size/volume of the hemangioma was calculated; change in color and other signs of involution were noted. We categorized the response to oral prednisolone into 3 grades: "Positive response" was considered when reduction in size/volume of hemangioma was 50% or more during the initial 4-6 weeks. In case of discernable but less than 50% reduction in size/volume, the effect was regarded as "possible or doubtful response". When no detectable change was noted, it was considered as "negative response". In the subset of patients having "negative response", the medication was stopped as soon it was apparent to have no effect on the lesions.

Results

In about 74% of patients (342 out of 462), the alarming hemangiomas were located in the head, neck and facial region. These lesions were often confluent and involved several adjacent areas. In 21% of cases (97 infants), the alarming hemangiomas were situated in the extremities. These, in most circumstances, were associated with complications and inflicted extensive areas of skin. Alarming hemangiomas involving perineal region and breast consisted 3% and 2% respectively (Table-I).

Table I. Distribution of alarming hemangiomas in the body (n=462).

Locations in the body	No. of alarming hemangiomas (%)
Face, Head and Neck	342 (74%)
Extremities	97 (21%)
Perineal region	14 (3%)
Breast	9 (2%)

Majority (71.6%) of the infants showed positive response in our study; that is, in 331 infants out of 462, there was more than 50% reduction in size/volume of the hemangiomas within 4-6 weeks of starting oral prednisolone. Ninety seven infants (21%) showed less than 50% reduction in size/volume (doubtful/possible response) and thirty four (7.4%) had negative response (Table-II).

Table II. Response of alarming hemangiomas to oral prednisolone therapy (n=462).

Treatment response	No. of infants (%)
Positive response	331 (71.6%)
Doubtful/possible response:	97 (21%)
Negative response	34 (7.4%)

A significant number of children (61%) developed puffiness of the face (Cushingoid facies) after 4-6 weeks of high-dose oral prednisolone (Table-III), Thirty seven children (8%) developed oral thrush and twenty three (5%) suffered from loose motion. Fungal infection of the skin occurred in 16 infants (3.46%) and frank abscess developed in seven (1.5%). Only two infants showed retarded growth and another developed pneumonia during the course of the treatment. None of the children developed hypertension, hirsutism or any symptom of peptic ulcer disease.

Table III. Occurrence of adverse effects encountered with oral prednisolone therapy (n=462).

Adverse effects	No. of infants (%)
Puffiness of face (Cushingoid facies)	282 (61%)
Oral thrush	37 (8%)
Loose motion	23 (5%)
Fungal infection of skin	16 (3.5%)
Abscess/Pustular lesioun	07 (1.5%)
Pneumonia	01
Retardation of growth	01

Discussion

In this study, we found that 71.6% of infants with alarming hemangiomas had positive response after oral prednisolone therapy. The success rate was higher than the rate achieved by Bartoszesky⁹, Stringel¹⁰ and Enjolres¹¹. The greater success rate in our study could be a reflection of the fact that while selecting patients with alarming hemangiomas, a protocol was strictly maintained to clinically differentiate between hemangiomas and vascular malformations and to exclude the latter which predicatively were unresponsive to oral prednisolone. The dosage schedule for treatment

of alarming hemangiomas deserves special mention. The recommended dose of oral prednisolone as suggested by Stenninger¹² was 2-3 mg /kg/day. However, recent investigations proved that a higher dose was likely to induce better result, and Sudan and Wolach¹³ recommended prednisolone in a dose of 4 mg/kg/day for no less than six weeks. From these works, we had used oral prednisolone in a dose of 2-4 mg/kg/day. This high-dose may be an additional reason for greater success rate achieved in the present study. But, surely, the search for an “optimum” dose of oral prednisolone for hemangiomas should continue and warrants further study.

This study also showed that about 21% of infants had “doubtful or possible” response. We chose such nomenclature because in these infants the reduction in size/volume of hemangiomas was relatively slow and lesser in magnitude, and we could not be sure whether the reduction was due to natural spontaneous regression or was induced by oral prednisolone therapy.

Finally, about 7.4% infants were categorized in the grade “negative response”. The exact cause for this unresponsiveness could not be determined but it might be speculated that these lesions could actually be vascular malformations and clinically we failed to distinguish them from hemangiomas. Mulliken and Glowacki¹⁴ in their study showed that clinically it was possible to differentiate hemangiomas and vascular malformations in about 85% of cases only.

The mechanism by which prednisolone induces or enhances regression of hemangiomas is not fully known. Many¹⁵ believe that prednisolone increases sensitivity to the circulating vasoconstrictive agents. Taubenhaus¹⁶ has postulated that prednisolone may alter formation of fibroblasts, ground substances and collagen to affect the growth of hemangiomas. The most revolutionary revelation has come from the research of Judah Folkman¹⁷ who proposed that hemangiomas, like all neoplasia, were angiogenesis-dependent and prednisolone inhibited angiogenesis to restrain growth of hemangiomas. This vasculogenic inhibition is effected by suppression of Vascular Endothelial Growth Factor-A (VEGF-A) by prednisolone.¹⁸



(a) Before treatment (b) Six weeks after treatment (c) Twenty weeks after treatment

Figures 1(a,b,c): Illustrate an infant with alarming hemangiomas and the response after oral prednisolone (with permission froms parents)

Regarding the adverse effects of prednisolone in our study, the most common complication (61%) was development of Cushingoid facies. The puffiness of the face was a transient phenomenon; as the dose was halved, the plethoric appearance had disappeared. The other complications were mild in nature. Only 3.46% of infants developed fungal infection of skin and 8% had oral thrush which was readily amenable to treatment. During our study, two infants were found to have growth delay and another developed pneumonia. For these patients, prednisolone was discontinued and appropriate treatment instituted to achieve complete cure. The untoward effects of prednisolone may always remain a concern - particularly about the unexpected long-term effects to a growing child. However, in the presence of a functionally disabling alarming hemangioma, we may consider such risk from prednisolone as being relatively low compared with the potential benefit it renders to these patients.

Conclusion

In summary, we can infer that for alarming hemangiomas, when no other treatment modality is suitable or feasible, oral prednisolone may offer substantial benefit to the majority of these moribund infants with life-threatening lesions. As a corollary, we may add with caveat that a number of transient complications may occur during the course of treatment but these are not more deleterious than the ailment itself for which the drug is being used- that is, the benefit certainly outweighs the probable risk.

Conflict of interest: None

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