Management of Alarming Hemangiomas with Oral Prednisolone in Infants
Choudhury KM\textsuperscript{a}, Hoque S\textsuperscript{b}

Abstract

\textbf{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.

\textbf{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.

\textbf{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.

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

\textbf{Key words:} Alarming hemangioma, treatment modality, oral prednisolone

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\textbf{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 Mulliken\textsuperscript{1}, 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 treatment\textsuperscript{2-4}. 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 trapping\textsuperscript{5}. Since than scientists used corticosteroids in various forms and routes\textsuperscript{6-8}. Intraliesional steroids and systemic or oral prednisolone achieved remarkable and consistent
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>
<thead>
<tr>
<th>Locations in the body</th>
<th>No. of alarming hemangiomas (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face, Head and Neck</td>
<td>342 (74%)</td>
</tr>
<tr>
<td>Extremities</td>
<td>97 (21%)</td>
</tr>
<tr>
<td>Perineal region</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Breast</td>
<td>9 (2%)</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Treatment response</th>
<th>No. of infants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive response</td>
<td>331 (71.6%)</td>
</tr>
<tr>
<td>Doubtful/possible response</td>
<td>97 (21%)</td>
</tr>
<tr>
<td>Negative response</td>
<td>34 (7.4%)</td>
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A significant number of children (61%) developed puffiness of the face (cushionoid 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).

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>No. of infants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puffiness of face (Cushingoid facies)</td>
<td>282 (61%)</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>37 (8%)</td>
</tr>
<tr>
<td>Loose motion</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Fungal infection of skin</td>
<td>16 (3.5%)</td>
</tr>
<tr>
<td>Abscess/Pustular lesion</td>
<td>07 (1.5%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>01</td>
</tr>
<tr>
<td>Retardation of growth</td>
<td>01</td>
</tr>
</tbody>
</table>

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 Bartoshesky\textsuperscript{9}, Stringel\textsuperscript{10} and Enjolres\textsuperscript{11}. 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 predricatively 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 Stenninger\textsuperscript{12} was 2-3 mg /kg/day. However, recent investigations proved that a higher dose was likely to induce better result, and Sudan and Wolach\textsuperscript{13} 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 Glowacki\textsuperscript{14} 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. Many\textsuperscript{15} believe that prednisolone increases sensitivity to the circulating vasoconstrictive agents. Taubenhaus\textsuperscript{16} 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 Folkman\textsuperscript{17} who proposed that hemangiomas, like all neoplasia, were angiogenesis-dependent and prednisolone inhibited angiogenesis to restrain growth of hemangiomas. This vascuogenic inhibition is effected by suppression of Vascular Endothelial Growth Factor-A (VEGF-A) by prednisolone.\textsuperscript{18}
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 overweighs the probable risk.

**Conflict of interest:** None

**References**


