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Efficacy of bleomycin treatment for symptomatic hemangiomas in children

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Abstract Five children aged 5–19 years had pain in massive, inoperable hemangiomas. They were treated with intralional injections of 2 mg bleomycin as a 0.4 mg/ml solution in the painful area. The injections were repeated after 4–6 weeks for a total of 6–10 times. All children were relieved of pain, and the swelling was reduced in all cases. There were no complications or side effects. Bleomycin therapy of painful, massive hemangiomas can be recommended in older children.

Key words Cavernous hemangioma · Pain · Bleomycin

Introduction

Most hemangiomas are not associated with symptoms, although a reddish or swollen appearance will cause cosmetic discomfort in some cases. The hemangioma is present at birth and grows during the first years of life. Coincident with growth, central thrombosis of the lesion will result in spontaneous regression during the first few years of life. At 5 years of age approximately 50%–80% of hemangiomas have resolved spontaneously [6, 7]. Hemangiomas are benign lesions, and malignant change is very unusual. On rare occasions they can cause severe complications because of locations in or near vital organs or tissues. Severe thrombocytopenia due to consumptive coagulopathy may occur, the so-called Kasabach-Merritt syndrome [1, 4]. Prompt therapy may sometimes be required to prevent serious disfiguration or grave complications [8].

Severe pain in a hemangioma is a complication that has not received attention, but may, especially in older children, cause severe discomfort and disturb normal activities. We have treated five children with severe pain in massive, inoperable hemangiomas by injection of bleomycin. This treatment modality and this specific indication have, to our knowledge, not previously been reported.

Materials and methods

The relevant data of the five children prior to therapy are shown in Table 1. The hemangiomas were widespread in all cases. The pain was located in the most swollen region. None of the children had any other malformation or disease.

Intralional injection with bleomycin was performed. After palpation and local skin anesthesia with EMLA cream, the painful area of the hemangioma was punctured using a 0.6 × 25-mm needle. The bleomycin was diluted in 5 ml saline and administered as a 0.4 mg/ml solution. Several deposits were made from the same skin puncture until a total of 2 mg bleomycin was injected. The injections were repeated after 4–6 weeks. Antibiotics were not given.

Local reactions such as painful swelling or redness were observed. Standard hematologic tests, but not coagulation studies, were taken before and after the treatment period. Magnetic resonance imaging (MRI) was performed prior to therapy in three patients and is planned after completed therapy. The size reduction was estimated by palpation in all cases, complemented by MRI in selected cases.

Results

The number of injections, effect of therapy, and results of the blood tests are listed in Table 1. MRI after finished treatment has only been performed in one patient to date, and showed reduced size of the hemangioma at the treated region. There was no local redness or sign of infection. No pulmonary disorders have been observed.

Discussion

Complete resection of massive hemangiomas has been regarded as difficult. In cases of severe complications, different nonsurgical treatment modalities have consequently been tried. High-dose corticosteroids have been
considered the primary treatment for controlling hemangiomas, but the response rate is only 30%–60% [2, 3]. Since 1989, hemangiomas have also been treated with alpha-interferon [11]. This requires a long treatment period, is very expensive, and the effect is uncertain.

Older children may sometimes report severe pain, especially during exercise, making it difficult to participate in an active, normal life. All five of our patients had this complication, combined in one case with a hemarthros of the knee joint that forced the child to use crutches. After four injections she could discard the crutches and begin physical exercise. On MRI 6 months after beginning the treatment, the size of the hemangioma was clearly reduced in the treated area. About 1 year later she complained of diffuse pain around the knee, but only after several hours on roller blades. For her, several years of painful discomfort were relieved within a few months of treatment that greatly improved her quality of life. The youngest child, patient 2, had hemangiomas extending from the pelvis to the foot in both legs. After four injections into the right knee, he could run and play without pain for the first time in his life. At palpation, the swelling around that knee was reduced. The main purpose of the treatment was to relieve the pain, and not to reduce the size of the hemangioma. It was of interest that the pain always decreased after four to five injections, before any size reduction could be noticed.

Bleomycin was discovered in 1966, and is an important anti-tumor agent [10]. Its antineoplastic activity is due to inhibition of DNA biosynthesis. It has also been recognized that bleomycin has a local sclerosing effect on the endothelial cells of the cyst wall of lymphangiomas. This histopathologic feature represents a mechanism of tissue repair with a nonspecific inflammatory reaction to bleomycin. Satisfactory therapeutic responses to local bleomycin treatment of cystic lymphangiomas were reported in 1977 [5, 12]. The injections resulted in reduction of the cystic mass in 86% of the 45 patients, and complete disappearance with or without persistent induration in 55% [9]. This promising result led us to try bleomycin in patients with symptomatic massive, inoperable hemangiomas. The maximum total dose of bleomycin given was estimated at 20 mg, corresponding to ten injections, in order to minimize the risk of side effects, especially pulmonary fibrosis. This maximum dose is about one-eighth of the regular total dose given for the treatment of Hodgkin's disease in older children. No pulmonary discomfort was noticed, but lung function tests were not performed.

The successful result in the first patient in our series led to further treatment of older children with pain from widespread hemangiomas. All the subsequent patients obtained pain relief as well as reductions in the size of the lesion. The mechanism the pain relief is unclear; the desired treatment effect of small, intrasional thrombosis will stop blood flow locally. The subsequent reduction in swelling and tension probably contributes to the disappearance of the pain. Due to the massive, diffuse extension, often with widespread components beneath the skin, the size reduction of the hemangioma was estimated by palpation of the most swollen and painful part that was treated with injections. It was, accordingly, often not possible to give an accurate size in centimeters. There were no skin complications, and the routine hematologic tests showed no abnormal values.

Although this series was small, the result of the treatment was uniformly successful. Guided by these observations, treatment with bleomycin can be recommended in older children with massive, inoperable hemangiomas of the capillary, cavernous, and mixed type where pain is a prominent complication. Even if visible size reduction is modest, there may still be relief of pain.

**Table 1** Sex, age, location, symptoms, number of injections, therapy effect, and hematologic data of the five patients treated with bleomycin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at presentation</th>
<th>Location</th>
<th>Symptoms</th>
<th>No. of injections</th>
<th>Therapeutic effect</th>
<th>Hematologic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>16 years</td>
<td>Right knee</td>
<td>Pain and hemarthros</td>
<td>10</td>
<td>Pain relief</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>5.5 years</td>
<td>Right and left extremities</td>
<td>Pain</td>
<td>8</td>
<td>Pain relief</td>
<td>No change</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>17 years</td>
<td>Left scapula</td>
<td>Left</td>
<td>7</td>
<td>Size reduction</td>
<td>No change</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>19 years</td>
<td>Left extremities</td>
<td>Pain</td>
<td>7</td>
<td>Size reduction</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>15 years</td>
<td>Left hip</td>
<td>Pain</td>
<td>6</td>
<td>Size reduction</td>
<td>No change</td>
</tr>
</tbody>
</table>

References