INTRALESIONAL BLEOMYCIN SCLEROTHERAPY FOR HAEMANGIOMAS: PROSPECTIVE CLINICAL STUDY FROM KASHMIR VALLEY


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Abstract

Introduction: Hemangiomas are benign neoplasms of endothelial cells and are the most common childhood tumor, occurring in 12% of infants. Clinically, these lesions can appear as an erythematous macular, a blanching macule, or an area of localized telangiectasia. MR imaging is the primary imaging technique in the evaluation. Bleomycin is used for sclerotherapy of hemangiomas.

Methods: This was a prospective study conducted in the Department of Plastic and Reconstructive Surgery at Sher-i-Kashmir Institute of Medical Sciences, Srinagar. Intralesional bleomycin was administered @ 0.2 to 0.6 units/kg body weight, and adjusting the volume roughly to around 0.5ml per 1cm² of the lesion.

Results: Cosmetic disfigurement was the most common chief complaint. Head and neck was the most commonly involved area (54.9%) followed by extremities (33.3%) and trunk (11.8%). Majority of the patients (56.9%) completed their therapy with 1 to 3 doses with a maximum of 8 doses in one patient. Majority of patients (84.33%) were satisfied with treatment.

Conclusion: Intralesional bleomycin is a highly effective modality for management of cosmetically disfiguring, non-resolving or large haemangiomas. The complication rate with this therapy is very low and patient satisfaction is high.

Keywords: Haemangioma, Bleomycin, Sclerotherapy

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Introduction
Hemangiomas are benign neoplasms of endothelial cells and are the most common childhood tumor, occurring in 12% of infants. Hemangiomas are found with greater frequency in girls, whites, premature infants, and twins.

Hemangiomas indicate endothelial proliferation and proceed through a two-stage process of growth and regression. Hemangiomas tend to be small and inconspicuous, with 60% absent at birth, and often are not initially noticed by parents and caregivers. Shortly after birth they undergo a proliferative phase, which corresponds to a rapid period of growth of endothelial cells that form syncytial masses with and without vascular lumens. In this phase, there is high expression of angiogenic factors such as vascular endothelial growth factor and basic fibroblast growth factor. They then undergo a stationary period, followed by a period of involution. The typical haemangioma will begin to involute approximately 10 months after birth and 50% of lesions are completely resolved in 5 years.

Clinically, these lesions can appear as an erythematous macular, a blanching macule, or an area of localized telangiectasia. During the proliferative phase, hemangiomas are high-flow lesions that are often revealed by bruit, pulsatility, and increased warmth. Hemangiomas can have deep, superficial, or mixed components. The clinical appearance of hemangiomas varies with the degree of dermal involvement and the depth of the lesions. A characteristic strawberry appearance is present when the lesions involve the skin. Deep hemangiomas, which do not involve the subcutaneous tissues, may have a blue appearance.

The two non-invasive imaging techniques that are most useful in the examination of vascular malformations or hemangiomas are MR imaging and sonography. MR imaging is the primary imaging technique in the evaluation (fig.1 and fig.2). The primary goals of imaging vascular malformations or hemangiomas include characterizing the lesion and discovering the anatomic extent of disease.

Many practitioners have advocated no therapy at all with the prescription that all hemangiomas will ultimately resolve. Recent studies have determined that late-involuting hemangiomas only incompletely regress and leave behind an often-significant residuum.

Neonates and infants may remain unaware of their disfiguring condition, but children 3 years and older are subjected to a burgeoning self-identity and the attendant social stigma that “being different” bears. A policy of watchful waiting in a slowly involuting haemangioma may prove detrimental to a child's psyche and may lead to ostracism from his peers.
Although hemangiomas are typically benign, a percentage of them develop life-threatening complications. Potential complications include Kasabach-Merritt syndrome (consumptive coagulopathy), compression of vital structures (e.g., airway, orbital structures), fissure formation, ulceration, and bleeding. These complications usually occur in the rapid proliferate phase and can be associated with a mortality rate as high as 20-30%. Numerous therapies have been used in an attempt to treat hemangiomas when complications develop during the proliferative phase. These regimes include high-dose steroids, α-interferon, and chemotherapeutic agents.

One of the mainstay treatments is systemic administration of corticosteroids. Approximately 30% of hemangiomas will respond dramatically to corticosteroids and another 40% will have some response. Unfortunately, the doses of corticosteroids required to treat hemangiomas are often associated with multiple side effects. These include severe irritability, weight gain, cushingoid appearance, growth delay, hypertension, diabetes, gastroesophageal reflux, and susceptibility to infections. Patients must be closely monitored for these complications.

When corticosteroid therapy fails to improve symptoms, other anti angiogenesis drugs such as α-interferon can be used, though some cases of irreversible neurologic spastic diplegia have been reported after its use; and is now used much less commonly to treat hemangiomas. Surgical excision, chemotherapy with vincristine sulfate, and embolization may be used in refractory cases. Laser therapy can be used to treat complications related to the superficial portions of the lesions such as ulceration, bleeding, and marked skin discoloration. Bleomycin is another agent introduced successfully more than a decade ago, for sclerotherapy of hemangiomas. Though, bleomycin has been reported to cause serious complications like pulmonary fibrosis when used at conventional dose for oncologic indications, it has been found safe when used for sclerotherapy of hemangiomas.

In our prospective study, we used this new agent, bleomycin, to evaluate its efficacy in treating hemangiomas.

Methods
This was a prospective study conducted in the Department of Plastic and Reconstructive Surgery at Sher-i-Kashmir Institute of Medical Sciences, Srinagar. The study included 51 patients diagnosed with hemangiomas, irrespective of age and sex, encountered in the department over a period of 2 years, from November 2009 to October 2011.

The patients were evaluated in detail. Detailed history was taken, patients' and/or attendant's concern noticed, and both general physical examination as well as local examination of the tumor was done.

Chief complaints like pain, bleeding, ulceration, fissure formation or cosmetic problem were noted. Besides, the compromise in various bodily functions caused by hemangiomas present in areas such as lips, tongue or orbital region was noted. Local compressive symptoms on vessels or nerves in areas such as in the neck region; or limitation of joint movement in areas such as elbow or fingers was also noted. All such patients were monitored for any functional improvement after sclerotherapy with bleomycin. The tumor was examined in terms of location, colour and surface, margins, dimensions, temperature, bruit and pulsatility.

Particular emphasis was laid on the determination of the volume of the hemangioma, which was done either by physical examination or with the help of radiological investigations, preferably MRI. USG and if required, colour doppler was done in cases of high flow hemangiomas.

Patients were taken for the procedure, after written informed consent. Intralosal bleomycin was administered (under local or general anaesthesia in infants and special
cases) in a fan shaped manner @ 0.2 to 0.6 units/kg body weight, not exceeding 15 units per dose, and adjusting the volume roughly to around 0.5ml per 1cm² of the lesion. One functional unit of bleomycin is equivalent to 1mg bleomycin. Some form of compression was applied immediately after intralesional injection of the drug, using either elastic compression bandaging in feasible areas such as limbs or scalp; or manual compression in other areas such as in face or trunk. Compression was maintained for a minimum of one hour. No prophylactic antibiotics were administered.

Patients with multiple hemangiomas were injected in only the most prominent lesion, while as other lesions were not injected. The patients were followed regularly and injected at 4 to 6 weekly intervals. Lesions were measured and photographed serially. Patients were given a maximum of 8 doses, after which the therapy was discontinued; and were followed up for a minimum duration of 6 months.

Complications, if any, arising out of bleomycin sclerotherapy were noted. These included flu like symptoms, cellulitis, hyperpigmentation, scarring and recurrence. Flu like symptoms or cellulitis was managed conservatively using antipyretic and/or antibiotics. Clinical examination of chest was done in all the patients and a chest radiograph was done at 6 months to look for any evidence of pulmonary fibrosis.

**OUTCOME was determined in terms of:**
1. Regression of volume in percentage:
   a) greater than 75% ---- Excellent
   b) 50 to 75% ---- Good
   c) 25 to 50% ---- Fair
   d) Less than 25% ---- Poor
2. Any complications:
   a) Cellulitis,
   b) Scarring,
   c) Hyperpigmentation,
   d) Recurrence
   e) Pulmonary fibrosis
3. Subjective satisfaction: Yes / No
4. Number of doses required for involution achieved in a particular case.
5. Duration of therapy.

**Results**
The patients in our series ranged from 5 months to 40 years and 51% were males.

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of patients</th>
<th>Number of lesions</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>Cheek</td>
<td>11</td>
<td>12</td>
<td>21.56</td>
</tr>
<tr>
<td>Lip</td>
<td>7</td>
<td>7</td>
<td>13.72</td>
</tr>
<tr>
<td>Arm, forearm</td>
<td>7</td>
<td>11</td>
<td>13.72</td>
</tr>
<tr>
<td>Neck</td>
<td>4</td>
<td>5</td>
<td>7.8</td>
</tr>
<tr>
<td>Finger</td>
<td>4</td>
<td>5</td>
<td>7.8</td>
</tr>
<tr>
<td>Hand</td>
<td>3</td>
<td>3</td>
<td>5.8</td>
</tr>
<tr>
<td>Lower limb</td>
<td>3</td>
<td>4</td>
<td>5.8</td>
</tr>
<tr>
<td>Abdominal wall</td>
<td>2</td>
<td>3</td>
<td>3.9</td>
</tr>
<tr>
<td>Chest wall</td>
<td>2</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Scalp</td>
<td>2</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Tongue</td>
<td>2</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>Genital (labia)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tip of nose</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Orbital region</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Shoulder</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td><strong>51</strong></td>
<td><strong>61</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

**Table 1: Showing distribution of cases as per site of involvement in our series.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>No of patients</th>
<th>Percent</th>
</tr>
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<tr>
<td>Nil</td>
<td>38</td>
<td>74.50</td>
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<tr>
<td>Flu like symptoms</td>
<td>3</td>
<td>5.8</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>2</td>
<td>4.0</td>
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<tr>
<td>Hyperpigmentation</td>
<td>6</td>
<td>11.76</td>
</tr>
<tr>
<td>Scarring</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>51</strong></td>
<td><strong>100.0</strong></td>
</tr>
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</table>

**Table 2: Showing Complications of Intralesional bleomycin sclerotherapy in our series.**

Cosmetic disfigurement was the most common chief complaint. Head and neck was the most commonly involved area (54.9%) followed by extremities (33.3%) and trunk (11.8%). Overall distribution of the patients with regard to their site of involvement is shown in table 1.

Multiple lesions were seen in 8 patients (6 cases with two lesions, and 2 cases with three lesions) involving the same site or part of the
body. Thus, a total of 61 lesions were present in 51 patients. Majority of the patients (72.5%) had received no previous treatment. Nine patients (17.6%) had received previous sclerotherapy with Sodium Tetradecyl Sulfate (STD), while 3 (5.9%) patients had undergone surgery and both of these groups presented with either recurrence or residual lesion. Two patients (3.9%) had undergone failed cryotherapy. Majority of the patients (56.9%) completed their therapy with 1 to 3 doses with a maximum of 8 doses in one patient. As the doses were repeated at 4 to 6 weeks interval, the duration in months roughly corresponded to the number of doses. Accordingly, the majority of patients (54.9%) completed their therapy in 1 to 3 months; while as another 31.4% cases took 4 to 6 months and 13.7% cases took 6 months for completion of their therapy.

Majority of patients (84.33%) were satisfied with treatment. No complications were seen in 38 (74.50%) cases while hyperpigmentation was the commonest complication seen in our series (table 2).

Discussion
Haemangioma is a disease of early age, predominantly seen in young females. From a series of 245 patients with 299 hemangiomas, Achauer et al reported that 173 were females and 72 males. A high female-male ratio was also found by Pienaar et al (female to male ratio 5:1) and Omidvari, et al, (female to male ratio 1.9:1). Female to male ratio in our series was 1:1 which can be explained on the basis of small study group under consideration. Majority (54.9%) of our patients had head and neck involvement followed by extremities (33.3%) and trunk (11.8%). Our study coincides well with those of Achauer et al and Finn et al. An even higher incidence (81%) of head and neck involvement was seen by Edwin. Majority (84.3%) of patients in our series had solitary lesions. Predominance of solitary lesions were also seen by Edwin et al, Oak et al, and Margileth.

Cosmetic problem was the most frequent concern of the patients and was present in 37 (72.54%) patient. This problem was the main concern in patients seen by Omidvari. Pain was present in four (7.8%) patients in our study in contrast to Omidvari where 25% of patients presented with pain. All the five children reported by Kullendorf presented with pain. In our study, no patient presented to us with complaints of bleeding or ulceration, proptosis, visual deterioration, astigmatism, dysphagia and respiratory obstruction. However, Sealy et al reported that out of 51 cases, the commonest symptoms were bleeding and a mass. The same study also reported serious symptoms which included bleeding needing blood replacement (1), proptosis (10), with rapid visual deterioration (4), dysphagia (3), and respiratory obstruction (2). Severe pain was a feature in two patients with large orbital lesions, both of which came to exenteration.

Excellent overall results were seen in terms of percentage regression in volume of haemangioma after bleomycin sclerotherapy. 60.8% patients showed excellent response who had an overall regression by 75 to 100% of which, 6 (11.76%) cases had nearly complete regression, and other 11 cases had more than 90.0% regression. A total of nine (17.6%) patients showed good response that had an overall regression by 50 to 75%, while another 9 (17.6%) patients had fair response with an overall regression by 25 to 50%. Remaining 2 (3.9%) patients had poor response with less than 25% regression. Nine patients, who had undergone prior sclerotherapy with STD, were separately analyzed for their response to bleomycin sclerotherapy. Seven out of nine had more than 75% regression, while 2 cases had less than 50% regression. Besides, in our study, all the patients who were less than 5 yrs age (11 cases) showed more than 75% regression.

Our observations regarding the regression in size of hemangiomas after bleomycin sclerotherapy goes in accordance with the results of various studies. Zheng et al found Bleomycin A5 was effective in all patients with strawberry and mixed hemangiomas, 91.2% of patients with cavernous hemangiomas, and 44.4% of patients with port-wine stain. Sarihan et al found that three out of 14 patients of complicated haemangioma completely regressed after only one bleomycin injection. Rest of the eleven patients had 60-100% regression during 6-14 months with two to three bleomycin injections. Kullendorf used Bleomycin in 5 cases of large inoperable hemangiomas and all the children were relieved of pain. Swelling reduced in all cases and there were no complications. Pienaar, et al found that out of
30 children who received Intralesional bleomycin, 22 had a response rate of greater than 75 percent, seven had 50 to 75 percent reduction in size of the hemangiomas and one child was judged to have a 25 to 50 percent reduction. Omidvari et al observed that after bleomycin sclerotherapy in 32 cases of complicated hemangioma, 70 to 100% regression occurred in 18 patients. Complete resolution of the lesion was seen in 56.0 percent after bleomycin sclerotherapy by Sainsbury et al in their series of 164 patients. Results of a study conducted by Muir et al and also coincide with the results of our study.

**Number of doses required and duration of therapy:**

In our study, patients were administered intralional bleomycin @ 0.2 to 0.6 units/kg body weight, not exceeding 15 units per dose, and adjusting the volume roughly to around 0.5ml per 1cm² of the lesion. One functional unit of bleomycin is equivalent to 1mg bleomycin. Completion of therapy was judged clinically and/or radiologically. Twenty nine (56.9%) cases completed their therapy with 1 to 3 doses, 18 (35.3%) cases received 4 to 6 doses while as 4 (7.8%) cases received more than 6 doses, maximum of eight doses. The injections; unlike STD sclerotherapy; were mostly painless, except in one case of haemangioma involving finger, where it was painful. The mean number of doses required per patient was 4 (3.745). This varied from just 1 dose given in two cases to a maximum of 8 doses given in one case.

Since the doses were given at 4 to 6 weekly interval, the duration of therapy roughly corresponded with the number of doses. Consequently, 28 (54.9%) cases completed their therapy in less than 3 months, other 16 (31.4%) cases completed their therapy in 3 to 6 months; while as 7 (13.7%) cases completed their therapy in more than 6 months.

The amount of drug used and the dosage frequency given to our patients were almost similar various other studies. Omidvari et al used the intralional injection of bleomycin every 2 weeks for four to six courses, at a dosage of 1 to 2 mg/cm² of the lesion (up to 0.2 to 0.4 mg/kg body weight). Similarly, Kullendorff evaluated the cases of massive inoperable hemangiomas who were treated with intralional bleomycin 2mg as a 0.4mg/ml solution in the painful area, and injections were repeated at 4 to 6 weeks intervals for a total of 6 to 10 times. Results achieved by him were also similar to ours.

In some of the studies, the total dose used in achieving the regression of hemangioma was higher than what we have used, yet the response rate was similar to ours. Pienaar C et al used a dose range of 1.4 to 24.6 mg and Muir et al administered a maximum dose of 3 mg/kg with no added benefits.

**Complications:**

Flu like symptoms were noted in 3 (5.8%) & cellulitis in 2 (4%) patients in our series. Muir et al also reported similar symptoms in their patients but with a slightly lesser incidence. Hyperpigmentation was the most common complication and was seen in 6 (11.76%) patients. Results of a study conducted by Muir et al and also coincide with the results of our study.

Complications:

- Flu like symptoms were noted in 3 (5.8%) & cellulitis in 2 (4%) patients in our series.
- Hyperpigmentation was the most common complication and was seen in 6 (11.76%) patients. Muir et al also reported similar symptoms in their patients but with a slightly lesser incidence.

Scarring and recurrence were noted in 1 (2%) patient each. Majority, 38 (74.50%), of patients did not show any complication during the follow period with us.

No patient in our study developed any serious complication like haematological toxic effects or pulmonary fibrosis or pulmonary hypertension, during the follow period with us. We performed the clinical examination of chest to look for any signs of pulmonary fibrosis and subjected the patients to chest radiographs at 6 months. Dose related pulmonary fibrosis is reported in patients who receive very high cumulative doses intravenously for oncologic indications. O'Sullivan et al found that the median time from the start of bleomycin administration to documented lung toxicity was 4.2 months (range 1.2–8.2 months). In their study, the factors independently predicting for increased risk of bleomycin pulmonary toxicity were GFR <80 ml/min, age >40 years, stage IV disease at presentation and cumulative dose of bleomycin.
bleomycin >300,000 IU. In our study, all the patients were less than 40 years of age; besides, the maximum amount of drug injected in a few cases was 15 units per dose, and maximum number of doses given wherever needed was 8, so in our study, the cumulative dose did not exceed 120 units in any patient.

Bleomycin hydrolase, present in all organs but in lower concentrations in skin and lungs, inactivate bleomycin. This may explain why the side effects are predominantly cutaneous and pulmonary, including pigmentation, alopecia and lung fibrosis. In the study of Muir et al, a mean of 3.4 sclerotherapy sessions were used. The maximum administered dose was 3 mg/kg. At such high dose, no systemic or pulmonary complications occurred. Besides, none of the other studies on bleomycin sclerotherapy in hemangiomas reported any case of pulmonary fibrosis during the follow up period.

We found that 39(76.5%) patients were satisfied with the response to treatment. This was due to the excellent response in terms of regression in size of haemangioma and added with simplicity and ease of the procedure. However, 12(23.5%) patients were not satisfied with the treatment, in view of multiple (more than six) doses needed, achieving only less than 50% regression in size of haemangioma, or in view of the pigmentation or recurrence.

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