






The Treatment of Lymphangiomas with Bleomycin in Childhood: A Retrospective Observational Study

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Abstract

Introduction: Lymphangioma is defined as the congenital malformation of the lymphatic system. According to morphological classifications, there are macrocystic, microcystic and mix types. Treatments vary from one clinic to another given that there are no commonly accepted guidelines. This study aims to present the results of ultrasonography-guided intralesional bleomycin treatment of lymphangioma.

Methods: Retrospective evaluation was conducted on 20 patients with lymphangioma who were treated with intralesional bleomycin. Under local anesthetic and aseptic conditions, 0.4-0.6 mg per kg bodyweight of bleomycin was injected under ultrasonography guidance. The response was graded as “excellent response” (>90% reduction), “good response” (>50% reduction in size) and “poor response” (<50% reduction or no change in size).

Results: The 20 cases comprised eleven female and nine male patients with a mean age of 3.1 years. The lymphangioma was located on the neck in eight cases, on the trunk in seven cases, on the axillary region in two cases, the mass extended from the neck to the mediastinum and retropharynx in one case. Also, it was on the anterior surface of the thigh in one case and on the anterior surface of the leg in one patient. Excellent response was seen in 50% of the patients, a good response in 40% and a poor response in one patient.

Discussion and Conclusion: Bleomycin injection is very effective for the treatment for macrocystic and mixed type lymphangioma of the neck and on any other surface area of the body. It is an appropriate treatment choice for cases that have previously undergone surgery and then show recurrence or incomplete resection.

Keywords: Bleomycin; childhood; lymphangioma; sclerotherapy.

Lymphangioma is defined as the congenital malformation of the lymphatic system. Defective connections of lymphatic ducts to the venous system, abnormal budding of lymphatic tissue and lymphatic sequestration that maintains the potential for regrowth are theories that have been proposed as potential causes of the disease [1–4]. Although lymphangioma may occur in any part of the body, it is most often seen in the neck and head. Lymphangioma usually develops at birth, but it can be seen at any age or even pre-

naturally by ultrasonography [5]. In patients with swelling and cosmetic deformity and suspected lymphangioma, ultrasonography is usually sufficient for diagnosis in experienced hands. Treatments vary from one clinic to another given that there are no commonly accepted guidelines. After the publication of successful results from many centres, the use of bleomycin treatment has increased. The present study aims to present the results of ultrasonography-guided intralesional bleomycin treatment of lymphangioma.

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Materials and Methods

A retrospective evaluation was carried out on 20 patients with lymphangioma who were treated with intralesional bleomycin between January 2012-July 2018. The diagnosis was reached on USG during a physical examination of the patients with suspected lymphangioma. Patients diagnosed with microcystic lymphangiomas (<1cm) were excluded from this study. Lymphangiomas with mediastinal and retropharyngeal components were visualized using Magnetic Resonance Imaging. The age, gender, weight, symptoms, lesion location and size, number of injections and dose were recorded for all patients.

Before each application, photographs were taken for ease of follow-up comparison. Under local anesthetic and aseptic conditions, 0.4-0.6 mg per kg body weight (depending on the size of the swelling) of bleomycin was injected with a 22 gauge intravenous cannula under USG guidance. The cyst fluid was not aspirated before or during bleomycin injection. When more than one cyst or septation was present, the calculated dose was divided according to the septae, and the divided dose was injected into these septae. This procedure was performed again after 2-4 weeks, if necessary.

Bleomycin injection was not applied to patients with lesions <1 cm in diameter or patients who completely recovered after the treatment. If intralesional bleomycin injections

were not successful after two injections, the treatment was terminated. The maximum cumulative dose of bleomycin was accepted as 5 mg/kg of body weight. The injection was performed by two pediatric surgeons, without the support of a radiologist, in the pediatric surgery clinic. Bleomycin injection was applied to the neck components only in patients with lesions extending to the mediastinum and retropharyngeal area.

Patients were observed for at least six hours following the procedure for possible acute complications of the treatment. The response was graded as "excellent response" (>90% reduction), "good response" (>50% reduction in size) and "poor response" (<50% reduction or no change in size). In one patient with a poor response to the procedure, Sirolimus was applied, and then, with no response to the medical treatment, this patient underwent surgery.

Results

The 20 cases comprised eleven female and nine male patients with a mean age of 3.1 years. The lymphangioma was located on the neck in eight cases, on the trunk in seven cases, on the axillary region in two cases, the mass extended from the neck to the mediastinum and retropharynx in one case, and was on the anterior surface of the thigh in one case and in the front of the leg in one patient (Table 1).

Table 1. Patients' data and treatment outcome

| n | Age | Gender | Location | Number of application | Response |
|----|-----------|--------|--|----------------------------|-----------------------------|
| 1 | 10 months | Male | Left chest wall | 4 | Excellent |
| 2 | 2 months | Male | Left chest wall | 2 | Excellent |
| 3 | Newborn | Male | Left cervical region, extending mediastinum to the hypopharynx | 2 bleomycin 2 sirolimus | Poor (Surgery underwent) |
| 4 | 1 month | Male | Posterior cervical | 3 | Good |
| 5 | 1 month | Female | Left cervical | 1 | Excellent |
| 6 | 6 years | Male | Right cervical | 3 | Excellent |
| 7 | 2 months | Male | Left cervical and submandibular | 4 | Good |
| 8 | 2 months | Female | Right axilla | 3 | Good |
| 9 | 3 months | Female | Right submandibular | 3 | Good |
| 10 | 2 months | Male | Left chest side wall | 3 | Good |
| 11 | 3 months | Female | Right upper abdominal wall | 3 | Good |
| 12 | 14 years | Female | Right supraclavicular | 1 | Excellent |
| 13 | 4 months | Male | Left chest and abdominal wall | 3 | Excellent |
| 14 | 3 years | Female | Right axilla | 2 | Excellent |
| 15 | 7 years | Female | Right supraclavicular | 3 | Excellent |
| 16 | 2 months | Female | Right cervical | 1 | Excellent |
| 17 | 3 years | Female | Right chest side wall | 3 | Good |
| 18 | 16 years | Female | Anterior surface of the right leg. | 4 | Good |
| 19 | 5 years | Male | Right breast | 3 | Excellent |
| 20 | 5 years | Female | Anterior surface of the right thigh | 2 | Excellent |

The patients received a minimum dose of 0.4 mg/kg; maximum dose of 2 mg/kg bleomycin. The total follow-up period ranged from four months to six years. Excellent response (Fig. 1) was seen in 50% (10/20) of the patients, a good response in 40% (8/20) (Fig. 2), a poor response in one patient (Fig. 3), and one patient did not attend follow-up appointments. A new-born patient who presented with a huge neck mass and had respiratory distress in the postnatal period was intubated in the Intensive Care Unit. USG examination of this pa-



Figure 1. Excellent response after bleomycin injection in two patients. **(a)** A-6-year-old boy. Three injections were administered. **(b)** A-2-month-old girl. Single injections were administered.



Figure 2. Good response after bleomycin injection in two patients. **(a)** A-2-month-old boy. Four injections were administered. **(b)** A-2-month-old boy. Three injections were administered.



Figure 3. Poor response after bleomycin injection in a new-born baby. Stiffness and intralesional hemorrhage were detected after the second injection. She underwent surgery.

tient revealed macrocystic and microcystic components of lymphangioma, which extended to the mediastinum. Magnetic Resonance Imaging revealed that the cyst extended from the anterior superior mediastinum to the hypopharynx. Two doses of bleomycin were administered to this patient at 2-week intervals. The bleomycin injection was unsuccessful. Stiffness and intralesional hemorrhage were detected after the second injection. Sirolimus was administered to this patient by the pediatric oncologist for one month, at a dose of 0.4 to 0.8mg/m² twice a day, adjusted to maintain sirolimus blood levels between 10 and 15 ng/mL. This treatment was unsuccessful, and the patient was transferred to another center on the family's request and underwent surgery there at age 1.5 months.

Surgical treatment had been previously applied to two patients in another center, and they were admitted to our center after recurrence. The first patient, aged eight years female, had a single cyst in the cervical, supraclavicular region and recovered after a single dose of bleomycin. The second patient, a 16-year old female, had scattered cysts on the anterior surface of the leg. A good response was obtained after three doses at 1-month intervals. Discoloration was seen in one patient and induration was observed in another patient.

Discussion

In addition to surgical treatment, sclerotherapy, radiotherapy, laser ablation, and cauterization therapy have been applied as interventional treatment of lymphangioma. Sildenafil, Propranolol, and Sirolimus treatment have been reported as oral medication therapy [6–8].

Due to the contiguity of the lesion with nerves and other important vessels, surgical excision of lymphangioma is usually difficult. Complete excision of the lymphangioma is difficult with high morbidity and mortality rates. Recurrence rates of large lymphangioma after surgical excision have been reported to be as high as 40%. Wound infection, hemorrhage, unsightly scar, serious postoperative fluid accumulations, facial nerve palsies, hypoglossal nerve paresis and lymphorrhea can also be seen. While lymphangioma has been treated with surgical methods in the past, intralesional sclerotherapy and oral medication therapy have become more common in recent years.

The first case of lymphangioma treated with sclerotherapy was reported in 1933, using sodium morrhuate. Since then, Ok432, iodine, ethanolamine oleate, ethylbloc, tetracycline, cyclophosphamide, bleomycin, boiling water, quinine, pingyangmycin, urethane, pure alcohol, sotradecol,

doxycycline, ethanol, sodium tetradecyl sulfate, acetic acid, and hypertonic saline have been used [1, 9–11]. Successful results have been published of the most commonly used treatments of Ok432 and bleomycin. After the first successful results of Ok432 injection treatment by Ogita et al. [12] further successful results have been reported in many series. However, as Ok432 is generally not available outside of Japan, it has not come into widespread use.

Bleomycin is an antineoplastic antibiotic with a sclerosing property, which was found during the treatment of malignant pleural effusion, and thereafter, inspired the treatment of lymphangioma. Intralesional injection of bleomycin in the treatment of lymphangioma was first used in 1977 by Yura et al. [13] Good results of bleomycin injection were reported in patients who had undergone previous surgery with incomplete resection and in patients with postoperative recurrence. Since then, many studies have been reported, and success rates have been reported varying from 35.7% to 91% for 'excellent response' and from 82% to 100% for 'good response' [14–17]. In the current study, an 'excellent response' to treatment was found in 55% of the cases and a 'good response' in 95% of the cases. These results were similar to other published series. Only one patient did not respond to treatment and surgical treatment was performed. Since intralesional bleomycin injection treatment was started in our clinic in 2011, bleomycin was applied to all patients with macrocystic and mixed type. Favorable results from the first treatments encouraged a continuation of the practice. The application was determined to be highly effective, with family and physician satisfaction. No serious life-threatening complications developed. In one patient, redness around the mass developed within 24 hours of the application and in one other patient, hardness in the mass. These symptoms recovered in 1–2 days with anti-inflammatory treatment. In another patient where the mass disappeared completely, discoloration of the skin was seen. This patient had a large mass in the cervical, supraclavicular region (Fig. 1). and partial improvement of the discoloration was seen at the 1-year follow-up examination. A noteworthy aspect of this study was that in two patients who had been treated surgically in other centers but had incomplete resection or recurrence, the lesion completely disappeared after the bleomycin treatment. This result was very pleasing for the families who had given up hope of treatment for their children. No major complications were observed in this study, demonstrating that bleomycin is safe for use in the pediatric population.

There is no clear textbook information about the dose to be administered. In many studies of bleomycin injection, it has

been administered at a dose of 0.3–0.6 mg/kg, which is far below the dose administered for chemotherapy [2, 9, 14, 17, 18]. In the present study, successful results were obtained at the dose of 0.4–0.6 mg/kg depending on the size of the mass. However, there is still a lack of clarity as to whether lower dose bleomycin would be successful in smaller lymphangiomas, and if so, at how small a volume. There is a need for further studies to investigate this subject.

Conclusions

In conclusion, bleomycin injection is very effective for treatment for macrocystic and mixed type lymphangioma of the neck and on any other surface area of the body. It is an appropriate choice for cases who have previously undergone surgery and then show recurrence or incomplete resection. Intralesional bleomycin can be considered for use as the primary modality until a better sclerosing agent or different treatment methods are found.

Ethics Committee Approval: The study was conducted in accordance with the 1964 Helsinki Declaration and was approved by the local ethics committee (Protocol No: 26/10/2018-164). Also, in the study, informed consent was obtained from the legal guardians of all individual participants.

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