Original Article

Our experience of bleomycin sclerotherapy for peripheral lymphangioma in children and review of the literature

Nandlal Kella[1], Prem Kumar Rathi[2], Ubedullah Sheikh[3], Mohammad Ali Qureshi[4]

ABSTRACT

Objective: To assess the efficacy of intralesional bleomycin in peripheral lymphangioma in children.

Methodology: This prospective study was conducted at the Department of Pediatric Surgery at Liaquat University of Medical and Health Sciences Jamshoro/Hyderabad from January 2005 to December 2009 .Patients included in this study were only with peripheral lymphngioma, while those with visceral lesions or previously operated for lymphangiomas were excluded. Diagnostic tools for lymphangioma were physical examination and ultrasound. All patients had aspiration of lesion with 20-24 gauge needle and intralesional injection therapy with bleomycin with dosage of 0.5mg/kg body weight diluted in normal saline. The procedure was performed as out patients. Patients were followed up at four weeks interval for up to six months. Personal data, procedure, complications and follow up were recorded on pre-designed proforma.

Results: Total number of patients included in this study was 20, with13 males and 7 females. Reduction in size was noted in 75%. Excellent response was seen in 9 (45%) patients who had cystic lymphangioma, while 6(30%) patients showed good response and 5(25%) had poor response. Common site was neck (65%).Transient increase in size of lesion and cellulitis were observed in three patients and treated conservatively.

Conclusion: Intralesional bleomycin is excellent in cystic lymphangioma, while it had good response in mixed lymphangioma. We suggest bleomycin as a primary therapy in all varieties of lymphangiomas.

KEY WORDS: Lymphangioma, Bleomycin, Treatment, Children.

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INTRODUCTION

Lymphangiomas are common congenital benign lesions resulting from the malformation of lymphatic system.[1] Incidence of lymphangioma is one in 6000-16000 live births, with no sex preponderance. About 60% of the lesions appear at birth, and 80% manifests within two years of life, or they may present at any time in life.[2] They are slowly growing tumors, and along with cosmetic effect, lead to morbidity and mortality because of compression of vital structures in neck and axilla, which are their common sites.

Though surgery still remains the mainstay of treatment, due to the risks of recurrence and damage to vital organs, as well as difficulties to excise the lesion completely, it is not believed to be an absolute procedure.[3] Various alternative therapeutic modalities have been opted, including laser therapy[4], interferon[5] and percutaneous sclerotherapy with

Correspondence:

Dr. Nandlal Kella,
House # 22 B al-Meeran Town,
Qasimabad, Hyderabad,
PAKISTAN.
E-mail: nckella@yahoo.com

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OK432, steroid, doxycycline, ethibloc and bleomycin.[6,7] But intralesional bleomycin has gained popularity as being easily available, economical, as well as efficacious non surgical treatment.

Bleomycin sulfate for injection is a cytotoxic glycopeptide antibiotic isolated from a strain of Streptomyces Verticillus. It exhibits a dual effect on human tissues, in that it can induce DNA degradation in undercoiled strand regions and in addition has a specific sclerosing effect on vascular endothelium.[8] In this study we are sharing our experience with intra lesional bleomycin in peripheral lymphangioma in children.

METHODOLOGY

This prospective study was carried out in the department of Pediatric Surgery at Liaquat University of Medical and Health Sciences Jamshoro/ Hyderabad Sindh, from January 2005 to December 2009. Patients included in the study were only with a peripheral lymphangioma, which were attended in out patient department or emergency. Excluded patients were those having intra abdominal or visceral lymphangioma and those previously operated for lymphangioma with recurrence.

Demographic data, site, size and type of lymphangioma, investigations, dosage of intra lesional bleomycin and follow up were recorded on predesigned proforma. All the patients had detailed history and physical examination. Investigations carried out were complete blood count, X-ray chest and ultrasound scan of lesion for size, extension and number of cysts and solid portion of lesion. The diagnosis was based on clinical examination and ultrasound scan.

Written informed consent was sought by Parents after counseling the mode of treatment, merits and demerits of procedure. The procedure was performed on out patient basis. After aseptic measures lesion was aspirated with needle (20-24 gauge), followed by intralesional bleomycin injection diluted in normal saline. The dose of bleomycin was calculated as 0.5 mg/kg body weight, while the amount of fluid injected depended on the size of lesion and amount of fluid aspirated from lesion.

The injection was repeated at four weeks interval with same dosage, with a maximum of three injections. Each patient had clinical assessment and ultrasound scan on each visit, to assess the size reduction of lesion. Photographs were also taken on each visit, for the sake of record keeping. The patients were followed on for six months; depending on how many times the injection sclerotherapy was needed, as well as the response of the lesion.

The response was graded as excellent (regression of lesion size> 90%), good (regression of size 50-90%) and poor (less than 10% or no response). Data was entered in SPSS 16 software for analyzing the frequency and percentage of patients.

RESULTS

A total of 20 patients were treated with intralesional bleomycin with age ranges seven days to 12 years. Out of 20 patients 13(65%) were male and 7(35%) were female with male, female ratio1.85:1. Most common site of lymphangioma was neck 13(65%).The detailed distribution of sites is shown in Table-I.

Reduction in size was noted in 15 (75%) patients, 9(45%) had excellent response while 6(30%) had good response. Five patients (25%) had poor response. Nine(45%) were cystic in nature having excellent response on bleomycin therapy, among them six had regression of lesion with one injection of bleomycin and three with two injections of intralesional bleomycin.

Eleven patients were mixed variety lymphangioma and had good and poor response depending upon the cystic component of lymphangioma. These

Table I: Showing distribution of site of lymphangioma.

Site	*Number*	*Percentage*
Neck	13	65%
Axilla	4	20%
Chest	1	5%
Back	1	5%
Parotid	1	5%

Table II: Comparison of results with intralesional bleomycin in lymphangioma.

Author	*No. of patients*	*Total size reduction*	*Excellent response*
Oxford et al [6]	16	84%	44%
Ikramuddin et al [16]	12	82%	75%
Saddle et al [17]	33	90%	30%
Tanaka et al [20]	47	87%	43%
Mahajin etal [21]	13	86.7%	53.3%
Mathur et al [24]	10	50%	33%
This study	20	75%	45%

patients were called for regular follow up with four weeks intervals. Cellulitis and transient increase in size was assessed in three patients respectively and were treated conservatively.

DISCUSSION

Treatment of lymphangioma is still a challenge to surgeon, and despite its associated morbidities surgery remains the most popular treatment.[9] Main goal of the treatment was the complete elimination of the pathology with minimal morbidity and mortality, that is less likely with surgery in head and neck region, where more than 75% of these malformation occur.[10] Hence attention was paid to search out a better alternative treatment. Various options have been tried, but sclerotherapy with different agents proved to be beneficial. Most commonly used sclerosing agents are OK432 and bleomycin. Acevedo et al[11] stated that OK432 is more superior to others having low complication rate, however in statistical analysis a significant difference between OK432 and bleomycin in regression of lesion was not demonstrated. Okazaki[12] was of the opinion that OK432 is not as effective as described in literature; however it has excellent role in single cyst and macrocystic lymphangioma. OK432 is not easily available and costly so its use in our set-up is very limited. Bleomycin gained popularity due to its safety, easy availability, being economical and lower complications.

Bleomycin is a cytotoxic antibiotic used in cancer therapy, discovered by Umezawa in 1966[13] and its role as an effective sclerosing agent in the management of lymphangima was described by Yura in 1977.[14]

Effect of Bleomycin depends upon the time duration for which the drug remains exposed to epithelial surface while it is almost independent of the lesion size. It is believed that if this is used in the form of microsphere oil emulsion, it will stay for a longer period at the site of injection and will have enhanced sclerosing activity.[15] Complete aspiration of lesion before sclerotherapy is recommended so as drug available per unit area is higher with a more sclerosing activity, while partial aspiration may dilute the drug in cystic lesion, as suggested by previous study.[16] Lymphangiomas having more cystic area would be more responsive to this therapy as suggested by Saddle[17], which is almost same in this study.

Dosage of bleomycin has been used variably in different studies ranging from 0.3-3 mg/kg.[16-18] In earlier study[7] it has been suggested that dose should not exceed 1mg/kg/dose or summated dose should not be more than 5mg/kg. In this study dose was 0.5mg/gk/dose, which is much lower to cause pulmonary complications while results were comparable to other studies.[7,16,19,20]

The number and time interval between sclerotherapy was variable ranging from 1-5 and two weeks to twelve weeks respectively.[20-22] In most of the cases cystic lymphangioma has responded in 1st and 2nd dose of sclerotherapy[12] which is almost same in this study. The reasons for less response might be mixed variety lymphangiomas, partial aspiration of lesion before sclerotherapy or variability of chemical constituents of lymphangioma fluid causing early metabolism or decreasing efficacy of bleomycin. These factors may need workup for consensus. OK432 is an immunostimulant agent that causes the body to attack the inner surface of lymphangioma by necrosis of epithelial cells. It has limited response on microcystic lymphangioma.

The male to female ratio found in our study was 1.85:1 that is almost same as in other study.[16] The commonest site of lymphangioma seen in our study was neck (65%) followed by axilla (20%) and this is also similar to other studies.[17,23] In this study reduction in size was noted in 75%, with excellent results (complete regression) in 45% only, which is comparable to other studies[6,16,17,20,21,24] as shown in Table-II.

Lungs and skin are more prone to complications by intralesional bleomycin, because of absence or low concentration of enzyme bleomycin hydrolase.[25] Pulmonary complications noticed with the chemotherapeutic agent bleomycin encompass a variety of pathological changes, including bronchiolitis obliterans organizing pneumonia, interstitial pneumonitis and progressive interstitial fibrosis.[26] Pulmonary fibrosis is most probably an immune mediated by tumor necrotic factor, a cytokine secreted by macrophages and lymphocytes. The risk factors for major pulmonary complications are; age more than 40 years, GFR less than 80ml/min, smokers or already compromised lungs, and when dose of bleomycin exceeds 30mg/m^2 or 4mg/kg body weight.[21,27] Ikramuddin[16] has suggested that bleomycin dosage may be adjusted, depending on the lesion size and quantity of fluid aspirated rather than weight of patient, keeping in mind the toxic dose of 4mg/kg/dose.

In this study, the complications were observed in only three patients, the fever and transient rise of lesion size, these observations are identical to other studies.[16,17]

CONCLUSION

Response of bleomycin as sclerosing agent is excellent in cystic lesion, while in mixed lesions it also has good response. Decrease in size of lymphangioma may make the subsequent surgery easier. So we suggest bleomycin as a primary therapy in all varieties of lymphangiomas.

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Authors Contributions:

Nandlal Kella: Conception, drafting and design and analysis of data.
Prem kumar Rathi: Drafting and final approval.
Ubedullah Shaikh: Acquisition and interpretation of data.
Mohammad Ali Qureshi: Analysis and drafting and final check.

Authors:

1. Dr. Nandlal Kella,
   FCPS Pediatric Surgery,
   Assistant professor,
   Department of Pediatric Surgery,
2. Dr. Prem Kumar Rathi,
   FRCS General Surgery,
   Assistant Professor,
   Department of General Surgery,
3. Dr. Ubedullah Sheikh,
   MS General Surgery Training,
   Rotational Trainee Pediatric Surgery,
4. Dr. Mohammad Ali Qureshi,
   Resident Pediatric Surgery,

1-4: Liaquat University of Medical and Health Sciences Jamshoro (LUMHS),
Jamshoro - Sindh,
Pakistan.