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ROLE OF INTRALESIONAL INJECTION OF BLEOMYCIN SCLEROTHERAPY IN THE MANAGEMENT OF PERIPHERAL LYMPHANGIOMA

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ABSTRACT

BACKGROUND: Lymphangioma is a benign hamartomatous lymphatic tumuor. The surgical excision remained mainstay of the therapy, but due to its infiltration along the nerves and muscles, total excision is not possible. In the present study, we have evaluated the clinical profile of all the cases of lymphagiomas coming to our hospital and evaluated the efficacy of intralesional bleomycin as a sclerosing agent in its management.

OBJECTIVE: To evaluate the effectiveness of the intralesional bleomycin as a sclerosing agent in the management of lymphangioma in children.

MATERIAL & METHODS: This study was performed at Khalifa Gul Nawaz Teaching Hospital Bannu from May 2011 to September 2013. A total of 12 patients including 7 males and 6 females with a ratio of 1.4:1, were treated with intralesional injection of bleomycin. The age range of the patients treated were 2 months to 12years. Those patients who had lymphangioma both macro- cystic and mixed type were included in the study. The microcystic variety and those patients who were treated surgically were excluded from the study. The diagnosis was based on clinical examination and ultrasonography. The dose used was 0.1- 0.5 mg/kg body weight. The patients selected were either on the parent's request to avoid general anesthesia and surgical complications or children with the lesion in an area where the surgical approach would be otherwise difficult and challenging and the surgical excision might lead in injuries to vital structures like nerves and vessels.

RESULTS: The overall success rate recorded as 75% which was significant. Ten patients responded to two injections while 2 patients received three injections. The response was assessed with 9(75%) out of 12 had complete resolution (Excellent response) and the remaining 3(25%) cases had partial (Fair) response only because of mixed macrocystic and microcystic lesions. There was no case with poor response.

We observed minimal complications and found post injection haematoma in one patient with a lymphangioma over the cheek and post injection abscess on the gluteal region.

CONCLUSION: Intralesional bleomycin injection is a safe and effective method for the treatment of lymphangioma. It is a preferable alternative to surgical excision in selected cases. This therapy may be used as primary modality instead of surgery in selected group of patients.

KEY WORDS: Lymphangioma, Sclerosing agent, Intralesional Bleomycin.

INTRODUCTION

Lymphangioma is a congenital malformation of the lymphatic vessels that belongs to a large spectrum of vascular malformations. It usually manifests at birth or before the age of 2 years. Incidence of lymphangioma is one in 6000-16000 live births, with no sex preponderance.[1] Sixty percent are seen at birth and 80-90% manifest by the age of two years. Some lymphangiomas grow steadily and may sometimes cause airway obstruction, feeding difficulties and cosmetic problems depending on its location. Recurrent inflammation and sudden haemorrhage are potential life threatening complications especially in cervico-mediastinal lesions. They are most commonly located in the head and neck region, and to a lesser extent in the axilla, inguinal region and

trunk, but can occur anywhere where the lymphatic vessels are there. Although benign lymphangiomas are frequently present with surgical difficulties and challenges due to their propensity to infiltrate and extend around neighboring structures. For many years surgery was the treatment of choice. However, encasement of adjacent structures such as nerves and vessels may result in nerve injury and other serious complications.[2]

Surgical excision has been the traditional treatment however incomplete resection, recurrence, possible injury to adjacent structures and surgical scars make it a less favorable option[3]. Complete resection is usually difficult due to its infiltration into the surrounding structures and incomplete excision may lead to lymphorrhea, wound infection and recurrence. Since the late seventies, various alternative therapeutic modalities have been opted, including laser therapy[4] Interferon[5] and percutaneous sclerotherapy to surgical excision. Intra-lesional sclerotherapy has been used successfully to achieve these goals using a variety of sclerosing agents.[6] Bleomycin is an anti-neoplastic agent and used in a variety of malignant lesions. It also has a local effect on the endothelial cells of the lymphangioma. The main concern in using bleomycin is the pulmonary fibrosis which is seen in patients getting higher doses and also depends on underlying pulmonary conditions. The chance of developing this complication is however negligible as very low dose is used for sclerotharpy[7]

We report our experience with intralesional injection of bleomycin in the treatment of lymphangioma. This study determines the efficacy of an antineoplastic drug bleomycin at a lower dose as a primary therapy for peripheral lymphangioma.

MATERIAL & METHODS

This study was performed at Khalifa Gul Nawaz Teaching Hospital Bannu from May 2011 to September 2012.

This was a prospective observational study of 12 successive cases of lymphangioma treated with percutaneous intralesional bleomycin sclerotherapy. The age range of the patients was between 2 months to 12 years. Male to female ratio was 7:5(1.4:1). Those patients who had lymphangioma both macro- cystic and mixed type were included in the study. The microcystic variety and those patients who were treated surgically were excluded from the study. The procedure was performed on approachable isolated peripheral subcutaneous lymphangioma. While patients who have lymphangioma of the deeper locations like mediastinal, spinal, abdominal or visceral lymphangiomas were excluded from the study. Patients who underwent primarily operative treatment were also excluded from the study.

The diagnosis of lymphangioma in these patients was made on the basis of clinical examination and ultrasound of the lesion. Ultrasound study was performed on all patients for diagnosis and for re-assessment after sclerotherapy. The tumour was classified based on the ultrasonographic appearance into three different subtypes: macrocystic, microcystic and mixed. CT or MRI was not performed in any case because the clinical assessment and ultrasound were sufficient to reach at a diagnosis. Patients' age, sex, body weight, symptoms, location and size of the lesion were recorded. Informed consent for intralesional bleomycin therapy was obtained from the guardian usually parents after counseling the mode of treatment, merits and demerits of procedure.

Under the effect of sedation and with strict aseptic technique, the cysts in lymphangioma were aspirated with a 22 or 24G canula with the patient using ultrasound guidance or sometimes blindly when this facility was not available. While keeping the tip of aspiration needle within a cyst lumen, 0.1 to 0.5 mg per kg body weight of bleomycin aqueous solution (1.5 mg/ml water) was injected. When more than one cyst was aspirated, the calculated dose was divided by the number of cysts aspirated and the divided

dose was injected into each cyst using more dilution with distilled water. A compression dressing, if feasible, was applied after the procedure. The parents were instructed to review with the child after 2 days in the outpatient department for removal of dressing and evaluation of any adverse effects. This procedure was repeated after 3- 4 weeks if the cystic component persisted and measured at least 1 cm in diameter. The injection was repeated at four weeks interval with same dosage, with a maximum of three injections. Though the recommended maximum cumulative dose of bleomycin used in the liteature is 5 mg/kg body weight but we didn't need the maximum dose for any case.

The procedure was performed as outpatient basis under sedation with chloral hydrate or under local anesthesia. Only three patients were admitted in the ward for 24 hours following the procedure for observation that had a big cystic hygroma at the neck for possible immediate complications of the treatment.

If the lesion could not resolved completely, it was reassessed with ultrasonography to see if further intralesional bleomycin was needed. The procedure was repeated according to the size of the cysts that measured at least 1 cm in diameter because intervention with a needle is possible in this size. The total number of injections and clinical response was recorded.

The response to the treatment was monitored by clinical as well as radiological judgment through US. The response was graded as complete resolution (total disappearance), good response (showing > 50% reduction in size) and poor response (showing < 50% reduction or no change in size).
After discharge, patients were followed up for 2 years at monthly interval for 6 months and 6 monthly for the rest of the period. No recurrence was observed in any case.

RESULTS

A total of 12 patients with lymphangioma were treated with intralesional bleomycin as a slerosing agent with the age range from 2 months to 12 years. All patients had a swelling due to a subcutaneous lesion. Male to female ratio was found 1.4:1.

The most common site of lesion was the neck 7(58.33%), followed by face 2(16.66%), axilla 2(16.66%), buttock 1 (8.33%). Lesions of the face were sited over the cheek. The number of injections per patient varied from 2 to 3 times, with a dose of 0.1 to 0.5 mg diluted bleomycin. The bleomycin was diluted with normal saline in a 1:4 ratio.

Table I: Showing distribution of site of lymphangioma

Site	Number	Percentage
Neck	7	58.33
Axilla	2	16.66
Face	2	16.66
Buttock	1	8.33

Ten patients responded to two injections while 2 patients received three injections. The follow-up period from the time of first injection ranged from 1 to 6 months. Though the intralesional bleomycin therapy was not failed in any patient but the response rate was different in different cases. The response was assessed with 9(75%) out of 12 had complete resolution (Excellent response) and the remaining 3(25%) cases had partial (Fair) response only because of mixed macrocystic and microcystic lesions. There was no case with poor response.

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

Author	No. of patients	Excellent response
Mathur et al[13]	24	33%
Tanaka et al[12]	20	43%
Ikramuddin et al[14]	12	75%
This study	12	75%

Some complications were also noted during the study. The post injection swelling on the cheek was observed in one case presented after a week and when re-aspirated it was blood stained fluid and labeled as post injection haematoma. One patient developed an abscess at the site of injection at gluteal region which was treated with antibiotic and surgical drainage was done. No patient developed excessive scarring as a result of the procedure except one patient with abscess who developed a dimple at the site of swelling after the successful treatment of the abscess with an incision and drainage procedure.

However no life- threatening complications such as respiratory obstruction due to pulmonary fibrosis and systemic hypersensitivity reactions to bleomycin were observed. There was no recurrence noted.

DISCUSSION

Lymphangioma is a diffuse lesion which remained a challenge for a surgeon during removal. It was found that lymphatic malformations spontaneously resolve when they became infected and the infection resolved. This fact led to the idea of the use of sclerosing agent. The first case of lymphangioma treated by sclerotherapy was reported in 1933, using intralesional injection of sodium morrhuate which resulted in complete regression of the lesion in 6 weeks.[8] Then a variety of sclerosing agents have been tried since that time like iodine, ethanolamine oleate, alcohol, ethibloc, tetracycline and cyclophosphamide, bleomycin and OK 432 with different results.[9] Bleomycin and OK-432 are the latest sclerosing agents currently in use. However, no studies in the literature are available to compare the efficacy between these two agents. Bleomycin is an antibiotic with anti-neoplastic effects, produced by the fermentation of streptomyces verticillus. It was discovered in 1966 and was found to inhibit DNA and RNA synthesis that cause single and double-strand DNA breaks. It has been used as an anti-neoplastic drug to treat malignancy.[10] It was observed during the treatment of malignant pleural effusion that bleomycin caused marked fibrosis and scarring. This sclerosing property was used for the first time in the treatment of lymphatic malformation in 1977.[11]

The literature has reported different results by different centers but there is a consensus of opinion that bleomycin is an effective sclerosing agent for macrocystic and mixed type of lymphangiomas.[12] Our experience confirmed that intralesional bleomycin therapy was very effective and our results are comparable to the published series. Different authors have reported success rates of between 40 to 75% for complete tumour regression, of up to 90% significant lesion regression, and poor response of between 15 to 20% using bleomycin.[12,13,14] We found 9 (75%) out of 12 with excellent response or complete resolution which accounts for 75% of the total number of the patients. While 3 (25%) responded partially with partial resolution (fair response).No case was found with a poor response.

The male to female ratio found in our study was 1.4:1 that is comparable to another study.[15] The most common site in our study was the neck (58.33%) which is also reported to be the common site(75%) in another study.[16] Dissection in the neck region is always challenging for a surgeon because of the deep penetrating nature of the lesion as well as important vital structures in the neck. Hence attention was paid to search out a better alternative treatment other than surgery.

The size of cysts remained the determining factor for the response of the lymphangiomas to the bleomycin as a sclerosing agent observed by some researchers during their study.[17] We also found that macrocystic and mixed type of lymphangiomas responded differently while the microcystic lesions were excluded from the study which were treated surgically because of known poor response in the literature.[17] That might be the reason that we received a good response during our study. The mixed lesions responded partially. However, the lesions reduced to a size that was cosmetically acceptable to the parents.

Dosage of bleomycin has been used variably in different studies ranging from 0.3-3 mg/kg[4,18]. In our study, diluted bleomycin mixed with saline as 0.1-0.5mg/kg was injected directly into a cyst after aspiration of the cyst fluid. Most authors advise against injecting bleomycin into the microcystic part or intraprenchymal component of the tumour because of the higher rate of systemic absorption which increases the risk of systemic toxicity. That is the reason OK-432 being safer than bleomycin after intraparenchymal injection[19]. But OK432 is not easily available and costly so its use in our set-up is very limited. However we did not observe such complication of bleomycin in our cases. The reason might be the selection of our cases which have macrocystic and mixed varieties of cysts where the chances of penetration of the drug into parenchymal tissues are rare.

No recurrence of tumour was observed in our study during our 6 months to 2 years follow up. Recurrence is defined as reappearance of the tumour after complete resolution or increase in size after initial significant reduction in size was seen .Though recurrence was reported in some studies[20]. The reason we did not observe any case of recurrence which might be because of the small sample size in our study. However the true rate of recurrences could only be ascertained if patients were followed-up for a longer period of time.

No serious complications were seen as a result of intralesional bleomycin therapy. Local abscess at the site of injection at gluteal region was seen in one out of 12 patients. The abscess presented 3 days after the first injection in one case. Incision and drainage was performed and later the lymphangioma resolved completely in that patient with some scaring because of the incision which was left open for secondary healing. The reason of abscess due to infection might be the poor aseptic technique and lack of proper sterilization facilities which is always to be blamed in our set up. One patient developed post injection haematoma on the left cheek one week after the procedure. It was aspirated and bleomycin reinjected. It may be due to injury to a vessel in the adjacent wall of the cheek. We did not need any support from any other team and all the patients were dealt on an outpatient basis. The literature mentioned some minor complications soon after intralesional injection of bleomycin like skin erythema, fever and transient cellulitis occasionally which in support of our findings[21].

In patients with complete resolution, there was no undesired excessive scarring or pigmentation noted at the injection site. Those patients who had excessive swelling of the skin had some wrinkles at the site of swelling after complete resolution. We believe that the aesthetic result from the use of bleomycin was as good as what was claimed from the use of OK-432[22].

The primary concern of bleomycin therapy is its risk of pulmonary toxicity. We did not observe any case with pulmonary fibrosis during our study. The reason might be the small size of our sample or shorter duration of follow up. The risk is dose related with an increased incidence associated with a total dose exceeding 400 i.u. or a single dose exceeding 30 mg/m2 of body surface area given intra-venous to oncology patient[22]. Elderly oncology patients and those with underlying pulmonary disease and renal failure were at greater risk. However, the doses used in sclerotherapy were much lower than those used for oncology purposes. Clinical studies from other countries and our own region did not report pulmonary fibrosis with intralesional bleomycin as a complication[2,3,23].

There was no report comparing the efficacy of the various sclerosing agents in a single study. Several published series were all review studies using a single agent. This would mean a very large number of cases need to be recruited and would involve many different centers. A single series of sclerotherapy treatment of lymphangioma usually would not achieve statistically significant results[23]. Looking at data of these small series together, however, may produce more concrete results. Solid conclusions

must therefore be drawn from reviewing many different series as a whole.

CONCLUSION

Local intralesional injection of bleomycin in children with lymphangioma is a simple, safe and effective method for subcutaneous lymphangiomas, with results comparable to surgical excision. It has the added advantage of avoiding inadvertent injury to vital structures, scarring and other complications of surgery. In the majority of cases, complete resolution may be achieved with two injections. No serious side effects from intralesional bleomycin therapy were observed. We recommend it as a primary therapy for all peripheral lymphangiomas and surgical treatment might be the last option for those cases where sclerotherapy had failed.

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