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Results of the Treatment of Cystic Hygroma with Intralesional Bleomycin Injection : A Preliminary Report in 20 Pediatric Patients

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Abstract

Introduction : **Cystic hygroma is a malformation of lymphatic vessels. Surgical excision is the treatment of choice but it has a high risk of recurrence and injury to the major organs. Bleomycin injection into the cysts can be used in cases of large cystic masses in order to avoid nerve injury and scar formation.**

Method : **A prospective study was performed during the period of 1992-1998. Twenty pediatric patients with cystic hygroma were treated with intralesional bleomycin injection. Fifteen were male and 5 were female. Their age ranged from 1 month to 11 years. Ten patients had recurrence of the disease post surgical excision before this management. The site of cystic hygroma was predominantly in the neck. The size of these lesions was larger than 5 cm in diameter in every case. After aspiration of the cyst contents, 3-10 mg of bleomycin was administered into the cavities. Repeated injections were performed at an interval of 2 to 6 weeks in some cases.**

Results : **An excellent response (complete clinical resolution) was obtained in 9 cases (45%). A good response (partial reduction of the size of the masses) was achieved in 7 patients (35%). A poor result (no clinical improvement) was noted in 4 cases (20%). Adverse reactions including fever, local swelling, redness and pain at the site of injection were found in 12 patients (60%) and they were present only for a few days . Leucopenia was noted in 3 infants below one year of age (15%).**

Conclusion : **Our data from this study suggested that intralesional bleomycin injection was an effective therapy in some cases of cystic hygroma. It should be used in the patients with large cystic masses, in which a surgical excision might be incomplete and risk of vital organ injuries may be high.**

Lymphangioma is a malformation of lymphatic vessels. It most frequently develops in the neck and axilla. Landing and Harber[1] classified lymphangioma into 3 groups : (1) lymphangioma simplex, composed of small capillary-sized lymphatic channels, (2) cavernous lymphangioma, comprising dilated lymphatic channels, often with fibrous adventitious covering, and (3) cystic lymphangioma or cystic hygroma, consisting of multiple cystic cavities filled with clear straw-colored fluid. Stal et al[2] divided lymphangiomas into 4 groups including capillary, cavernous, cystic and hemolymphangioma. Most of lymphangioma which occurs in the children is cystic hygroma. The terms "cystic hygroma" and "lymphangioma" are often used interchangeably, and described a spectrum of benign cystic tumors of the lymphatic system.[3] Surgical excision is the treatment of choice in patients with cystic hygroma but it is very difficult because of infiltrative nature of the multiple cysts to the surrounding organs. Complete excision cannot always be accomplished and recurrences commonly occur after surgery.[3-7] Risks in surgical removal of cystic hygroma include vital organ

injuries, bleeding and infection. Alternative methods of treatment such as radiation therapy and injection of sclerosing agents had been tried but the results were not satisfactory.[8-10] Yura was the first clinician to use bleomycin solution as a sclerosing agent for treatment of lymphangioma.[11] The results were effective but not so in other types of lymphangioma. At our institute, most pediatric patients with cystic hygroma underwent surgery. Some cases had recurrences and postoperative morbidity. This report described our initial study of cystic hygroma treatment with bleomycin injection in the recurrent and high-risk cases in the recent years.

Materials and Methods

A prospective study was performed during the period of 1992-1998. Twenty children with cystic hygroma were treated with bleomycin injection into the lesions. Fifteen were male and 5 were female. The age at treatment ranged from 1 month to 11 years. Twelve of them (60%) were below one year of age. Of the 20 patients, 10 had recurrences of the disease after previous surgical removal and 10 received bleomycin injection as an initial therapy. The size of lesions were larger than 5 cm in diameter in every case. The site of cystic hygroma was predominantly in the neck (Table 1). Fourteen patients (70%) were admitted before the beginning of treatment and the 6 remainders (30%) were managed in the operative room of the out-patient unit. Complete blood count was done before the procedure and 3-7 days after drug administration.

Bleomycin was prepared as a solution of 1 mg/ml in normal saline solution with a sterile technique. The treatment was performed in the operative room under general anesthesia in young patients and local anesthesia in older children. After aspiration of the cyst contents, bleomycin solution was administered into the cyst cavities. A dosage ranged from 3 to 10 mg per injection (0.6-1 mg/kg, maximum of 10 mg). Injections may be repeated at an interval of 2-6 weeks depending on the outcome of the achievement. The total dose of bleomycin in each patient ranged from 5 to 50 mg, in 1-8 injections.

The criteria for clinical responses followed former reports.[12,13] An "excellent" response was determined if the masses disappeared completely or almost completely with slight residual induration. A "good" response was indicated if the masses diminished remarkably (over 50% reduction), with some residual lesions. A "poor" response was used in the cases in which the masses diminished slightly or remained the same size.

Table 1 Clinical data of the 20 patients.

Clinical data	Numbers	Percent
1. Sex incidence		
male	15	75
female	5	25
2. Age incidence		
1 month - 1 year	9	45
> 1 year - 3 years	4	20
> 3 years	7	35
3. Status before this therapy		
recurrence post excision	10	50
primary treatment	10	50
4. Sites of the lesions		
face	2	10
neck	5	25
neck, cheek, floor of mouth and tongue	7	35
neck, axilla, mediastinum and arm	1	5
axilla	1	5
arm and forearm	2	10
abdominal wall	2	10

Results

Intralesional bleomycin injection produced satisfactory results in 16 of the 20 patients (80%). An excellent result (Figures 1-3) was obtained in 9 cases (45%). Two required only single injection. The cyst contents could be easily drawn from the cavities in large quantity in all of them. Reduction in size of the masses was usually achieved by 2 weeks to 2 months. There was no recurrence during the follow-up period of over one year. A good result (Figure 4) was obtained in 7 cases (35%). In three of them, the tumors recurred and they underwent surgery. A poor result was noted in 4 cases. Two patients received two injections and were lost to follow-up without clinical response. The remaining 2 cases underwent surgery and only palliative resection was performed. The details of clinical response, drug administration and various site of the tumors were summerized in Table 2.

Minor side effects of bleomycin injection in-

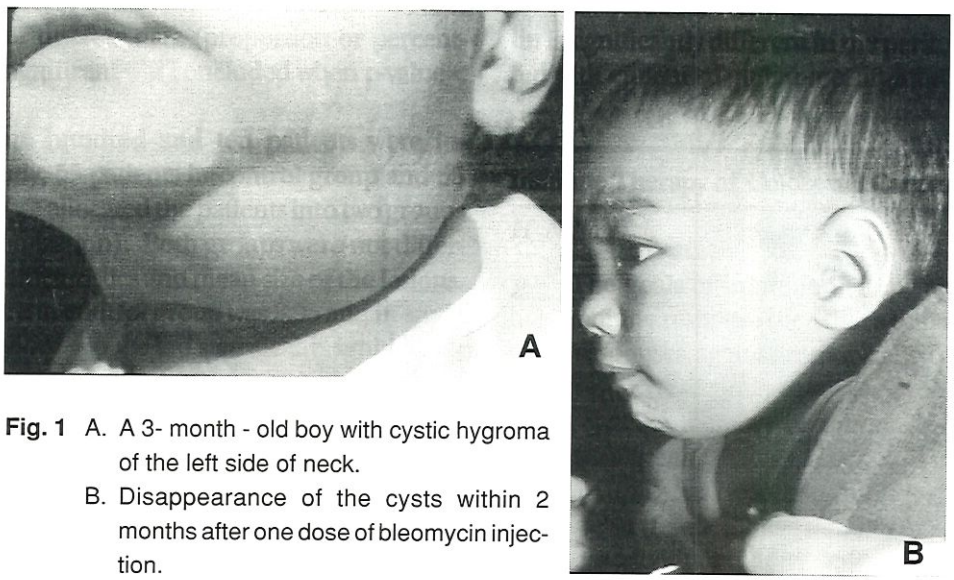

Fig. 1 A. A 3- month - old boy with cystic hygroma of the left side of neck.
B. Disappearance of the cysts within 2 months after one dose of bleomycin injection.

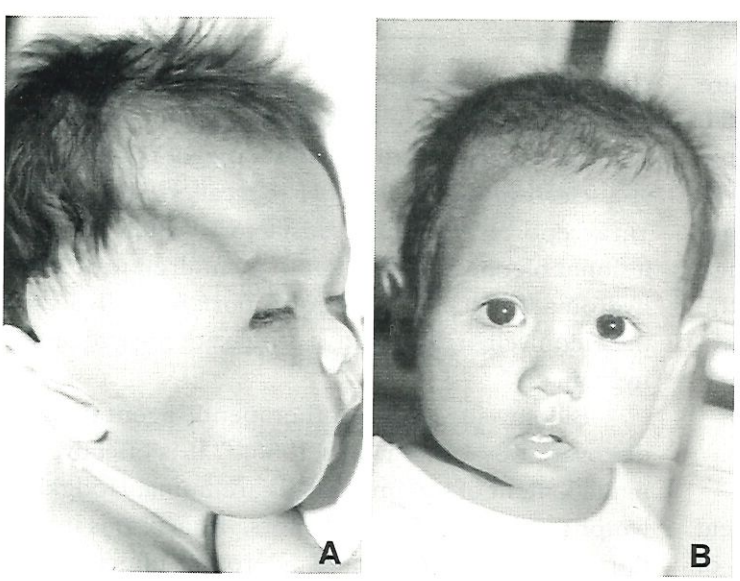

Fig. 2 A. Cystic hygroma of the face in a 8 - month - old boy.
B. Excellent response within 3 months following 3 doses of bleomycin injection.

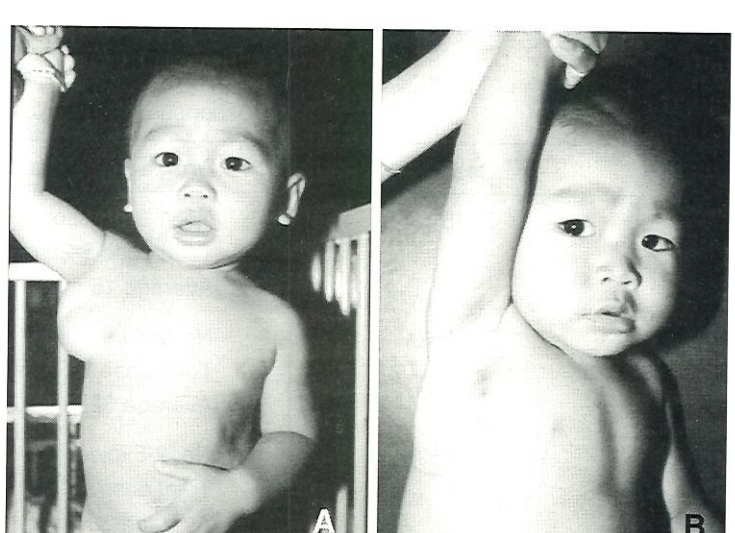

Fig. 3 A. A cystic mass of the right axilla in a 1-year-old boy.
B. Complete regresstion of the mass within 2 months after 2 doses of bleomycin injection.

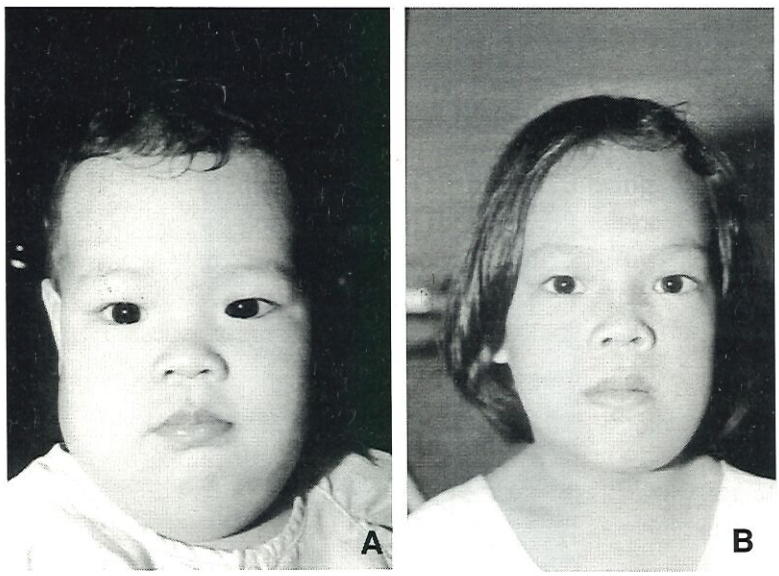

Fig. 4 A. An 11- month - old girl with cystic hygroma involving neck, cheek, floor of mouth and tongue.
B. Good response of the neck lesion and partial reduction of the lesions in floor of mouth and tongue.

cluding local swelling, redness, pain and fever were seen in 12 cases (60%). They were present within 24-48 hours after injection and continued for a few days, Leucopenia was noted in 3 infants below one year of age. The white blood cells were decreased to about one half of the initial examination and they returned to normal limit within 2 weeks after drug administration. None of our patients developed pulmonary fibrosis during this study.

Discussion

Several non-surgical methods were used to treat cystic hygroma or lymphangioma, however none of these procedures were satisfactory.[8,10] Surgical excision is still advocated as the treatment of choice, although it has high risks of recurrences, injuries to nerve and blood vessels, infection and scar formation. A non-surgical technique involved the use of bleomycin as a sclerosing agent in order to treat cystic hygroma. Yura reported the first satisfactory result of intralesional bleomycin injection in 4 children with cystic hygroma.[11] Since 1978, several reports have advocated the bleomycin treatment as a primary therapy for cystic hygroma.[12-16]

Bleomycin is a chemotherapeutic agent that was discovered by Umezawa in 1966.[17] It is effective for management of squamous cell carcinoma, Hodgkin's lymphoma and testicular tumors. Its action is inhibition of DNA synthesis and sclerosing effect on endothelial cell of cystic hygroma. It is believed to result in cystic regression by direct action on the lymphatic

Table 2 Clinical responses of bleomycin treatment for cystic hygroma.

Results	Cases / Percent	Drug administration	Locations
Excellent	9 (45%)	No. 1-3 injections Total dose 5-25 mg. Average 15 mg.	Face (2), neck (3) axilla (1), arm (1) abdominal wall (2)
Good	7 (35 %)	No. 2-8 injections Total dose 7-50 mg. Average 32 mg.	Neck (1), neck cheek, floor mouth and tongue (5), forearm (1)
Poor	4 (20%)	No. 2-5 injections Total dose 15-35 mg. Average 28 mg.	Neck (1), neck, cheek, floor of mouth and tongue (2), neck, axilla, mediastinum and arm (1)

Table 3 Review results of the treatment of cystic hygroma with intralesional bleomycin injection.

Authors	Bleomycin injection	Results (%)		
		Excellent	Good	Poor
Tanigawa N, et al, 1987[12]	In oil emulsion	39	42	19
Tanaka K, et al, 1990[15]	In oil emulsion	43	44	13
Okada A, et al, 1992[13]	In water soluble	55	33	12
Orford J, et al, 1995[16]	In oil emulsion	44	44	12
Queen Sirikit National Institute of Child Health, 1999	In water soluble	45	35	20

endothelial lining and producing an inflammatory process.[13] Bleomycin was originally prepared in oil emulsion for management of lymphangioma and the successful rate of excellent and good results was in about 80%.[12] Okada et al used bleomycin in normal saline solution instead of oil emulsion and received the same satisfactory results[11] (Table 3). Our preliminary study demonstrated that bleomycin in normal saline solution could be used in treating cystic hygroma with the favorable rate of 80% and complete disappearance in 45% of the cases.

Patient selection for this procedure was important. It was more likely to produce a size reduction in cases of large superficial cystic lesions than in other forms of lymphangioma. Cervical, facial and axillary lymphangiomas were mainly composed of a cystic type which were suitable for aspiration of sufficient volume of lymphatic fluid before bleomycin injection. This was supported by the literature[10-14] as well as this study. According to our observation, cystic hygroma that involved deep tissue of cheek, floor of mouth, tongue and mediastinum, did not response well to this mode of therapy. The results were only partial reduction in some cases.

Side effects experienced from this study included transient swelling, redness at the site of injection, pain and fever. They developed within 24-48 hours after injection and continued for a few days. The swelling might result in airway compression in a cervicomediastinal cystic hygroma. Tanaka et al suggested that symptomatic cystic hygroma of neck and mediastinum was the contraindication for intralesional bleomycin injection.[15] Other minor side effects including nausea, vomiting and diarrhea were not present in our patients. We found leucopenia in 3 patients below one year of age. We believe that the dose of 0.6-1 mg/kg of bleomycin might be too high for young children and reflected in bone marrow suppression. The dosage should be reduced in infants. Pulmonary fibrosis was the most serious side effect of bleomycin therapy in malignant tumors. The risk was related to the dose with an increased incidence at a total dose of more than 400 unit (mg), or a single dose exceeding 30 mg/square meter.[18] Patients with underlying pulmonary diseases were at risk. This complication has not been found in the treatment of children with cystic hygroma from other reports[11-15] because these pediatric patients usually do not have underlying pulmonary disease and the doses are probably far lower than those used for oncologic purposes. Okada et al[11] suggested that bleomycin in normal saline solution should be used for cystic hygroma management in a dose of less than 1 mg/kg and at an interval of at least 2 weeks. The total dose should be limited to 5 mg/kg in each patient. With this restriction, pulmonary fibrosis may be avoided in children.

Conclusion

This study was our initial experience for the treatment of cystic hygroma with intralesional bleomycin (in normal saline solution) injection at the Queen Sirikit National Institute of Child Health during the period of 1992-1998. Twenty children were treated by this regimen and satisfactory results were obtained in 80 per cent of the cases with minor side effects.

Available data from this study suggested that intralesional bleomycin injection was an effective alternative method for cystic hygroma therapy in some selected cases, although surgical excision is probably the treatment of choice in most cases. Bleomycin was

suitable for recurrent cystic hygroma and in the case with very large cyst in which surgical removal might be incomplete or might have high risk of damage to nerves and blood vessels.

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