Bleomycin Sclerotherapy for Management of Cervicofacial and Axillary Lymphatic Malformations in Children

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ABSTRACT

Background and Aim: *Lymphatic malformationscan result in severe functional and aesthetic disorders, due to their progressive growth and affinity to occur in challenging anatomical regions as the head and neck region and the axilla. Intralesional sclerotherapy may serve as a single treatment or as an adjunct to surgery.This study presents our early experience with intralesional bleomycin injection in the management of axillary and cervicofacial Lymphatic malformations, over an initial period of 12 months.* ***Methods:*** *This prospective study was conductedat the department of Pediatric Surgery of Cairo University Specialized Pediatric Hospital (CUSPH) and included 8 patients whopresented with lymphatic malformations and were all treated with intralesional bleomycin injection. The dose of bleomycin inject was adjusted to 0.5 IU/kg/injection, with 4-weeks intervals, for 3 – 5 cycles.* ***Results:*** *The median age at inclusion and initiation of treatment was 3.2 years.The average number of sessions was 3.5 ± 0.5. Overall, a satisfactory response was detected in 87.5% of the cases (n = 7), among them one case had recurrence. No systemic adverse effects were noted.* ***Conclusion:*** *Intralesional Bleomycin injection is a safe and effective modality for treating cervicofacial and axillary lymphatic malformations in the pediatric age group.*

Keywords: *Bleomycin; Sclerotherapy; Intralesional Injection; LymphaticMalformations*

INTRODUCTION

Lymphatic malformations (LMs) are developmentalanomalies of the lymphatic system, consisting of abnormallyformedlymphatic channels and cystic spaces, lined with endothelium.[1] Although there are many management modalities and protocols for LMs, yet surgery remains the mainstay for successful management. However, surgery may harbor many difficulties such as the difficulty or inability of complete excision, bleeding, injury of nearby important neurovascular structures and scarring. Therefore, the intralesional injection of sclerosing agents evolved in three different directions; as a preoperative management to help in reducing the lesion size; as a postoperative solution for residual lesions;or as asingle treatment modality. [2]

Many sclerosing agents are available including ethanol, 5% ethanolamine oleate, 3% polidocanol, and bleomycin.All have been proven to be effective. Also, new sclerosing agents are developed continually, such as foam preparations (sodiumtetradecyl sulphate). One of the most commonly used agents is absolute ethanol due to its low cost, antiseptic quality and low associated recurrence rate. However, complications with it occur at a high rate, such as skin ulceration, nerve atrophy, and systemic complications. [3]In 1966, bleomycin was developed as a cytotoxic anti-tumoragent by Umezawa.It exhibits a specific effecton the vascular endothelial cells through a nonspecific inflammatory reaction resulting in occlusion of vessels.[4]

In this study, we present our center's experience with intralesional bleomycin injection in the management of LMs, evaluating the clinical outcome, efficacy and the potential complications.

METHODS

This prospective study was conductedthrough the vascular anomalies' clinic of Cairo University Specialized Pediatric Hospital, between January 2016 and January 2017. It includes 8 patients whopresented with LMs and were all treated with intralesional bleomycin injection.

Prior to starting the treatment, an informed consent was obtained from all the candidates and an ethical approval was obtained via the departmental research ethics and scientific committee. A standardized set of data was recorded in a specified sheet including age, gender, site and size of the lesion, clinical history,

dosage and timing of injections, clinical response, side effects and findings at each follow up visit.

The diagnosis was established as a LM after clinical evaluation by a consultant pediatric surgeon and confirmed by radiological studies in the form of ultrasonography (US) and magnetic resonance imaging (MRI).

The treatment protocol

Under complete aseptic conditions, and ultrasound guidance for deep lesions, intralesional injection of bleomycin was done at a dose of 0.5 IU/kg/injection, with 4 weeks intervals, for 3 – 5 cycles. The maximum dosage was 15 IU/injection. Preparation of the solution was done with 0.9%saline in the form of 15 mL normal saline for each vial of 15 IU (1 IU/mL). Before injection, aspiration was done. All the cases were injected by the same operator.

Clinical response was evaluated according to the following criteria: complete response (complete disappearance of vascular tissue), marked improvement (>70% disappearance of vascular tissue), moderate improvement (40–70% disappearance of vascular tissue), slight improvement (<40% disappearance of vascular tissue)and no response. [3]

Follow up was done in 4-weeks' intervals along with injection sessions, until no more intervention was needed. Further follow up was arranged every 3 months,until 1 year passed from initiation of the therapy. Two independent blinded examiners evaluated the images, to assess the degree of improvement contrasted to the baseline images prior to starting the injections.

RESULTS

Eightpatients were managed with serial injections of intralesional bleomycin with a median age of 3.2 years (range: 11 months to 8 years). Twomales and 6 females were included in the study. The average number of sessions was 3.5±0.5. ***Table (1)*** summarizes patients' demographics and clinical response.

Table (1): Demographic and clinical data.

Case no.	Age(yrs)	Sex	Site	Size(cm)	No. of sessions	Outcome	Surgery	Follow up (m)
1	4	F	Lt. Cheek	2*2	3	Marked Improvement	Nil	6
2	8	M	Rt. Cheek	3*2	3	Marked Improvement	Nil	8
3	1.4	F	Rt. Neck	3.4*1.3	4	Marked Improvement	Nil	6
4	11 m	F	Rt. Axilla	7*8	4	Complete Resolution	Nil	10
5	4	M	Rt. Parotid	5.5*4	4	Marked Improvement	Nil	4
6	2	F	Rt. Neck	5*3.2	3	Slight Improvement	Nil	12
7	3.5	F	Neck	8*9	3	No Response	Partial excision	6
8	2	F	Lt. Axilla	4*3	4	Complete Resolution	Nil	7

Abbreviations: (LM) lymphatic malformations, (m) months, (yrs) years, (cm) centimeter, (Lt.) left, (Rt.) right.

Regarding the clinical response,two (25%) out of the 8 patients showed a complete response. Marked improvement was detected in four cases (50%). One case (12.5%), showed slight improvement. Only one case (12.5%), showed no response to treatment. This malformation was in the neck region.

With regards to the adverse effects, two cases (25%) showed signs of infection (managed with topical antibiotics),and one case showed recurrence.

Figure (1): 8 years old male with right check LM after 3 cycles of injection, showing marked response.

DISCUSSION

Throughout the literature, there is no consensus upon a single modality for the management of LMs. Surgery offers an ideal solution for small and localized lesions; however, with lesions in the head and neck, the axilla or markedly large lesions, de-bulking may be feasible bearing in mind the potential risk for injuring the adjacent vital structures, scarring and functional losses (due to a combination of all above issues). [6]

Historically, various sclerosing agents were provided for treatment of LMs, such as hypertonic solutions, surfactants, and detergents. However, none of them showed superiority regarding the treatment of vascular lesions. Familiarity of the treating surgeon or interventional radiologist, availability of the sclerosant, cost and affordability, site and morphology of the vascular lesions are among the factors that influence the choice of the sclerosing agent. [2]

Owing to its availability and low cost, ethanol is the most widely used sclerosing agent. However, it poses a risk of adjacent tissue damage, due to the high neural and mucosal tissue sensitivity to ethanol, as well as alcoholintoxication. Sodium tetradecyl sulfate(STS), an anionic surfactant, has the advantageof efficacy at low concentrations.Compared to ethanol, it is less cytotoxic. However, with extravasation, it may cause thrombosis and skin necrosis.Ethanolamine has the advantage of being less cytotoxic, but it hasa deleterious adverse effect on the kidneys. [7]

Bleomycin was introduced by Umezawa in 1966, as a cytotoxic antitumor antibacterial agent that was used in the successful treatment of lymphoma and testicular tumors. In 1977 *Yura et al*. reported their success in the management of lymphatic malformations by intralesional injection of bleomycin. It induces DNA degradation resulting in apoptosis of rapidly proliferating cells, as well as a sclerosing effect on vascular endothelial cells. [7]

Systemic side effects of bleomycin were reported in oncology patients with intravenous injection such as nausea, vomiting, and interstitial lung fibrosis, in toxic doses. However, with intralesional injections, those adverse effects are minimal with only one described case of pulmonary toxicity in an excess of 2600 patients reported in the literature. [4] In our series, and within the limitation of the study duration and being an early outcome report, there were nocases suffering from pulmonary side effects following intralesional bleomycin injection.

Recently, many studies reported the efficacy of bleomycin as a therapeutic agent in treating vascular malformations, response rates range

between 40% and 100%. [5] In this study,six cases(75%)showed a response of more than 70% tissue reduction to the bleomycin injections, which is comparableto the available literature. About 87.5% showed noticeableresponse to this therapy and only one case (12.5%) did not show any response at all and was managed by a partial surgical excision. This lesion was occupying the cervicofacial region.

Spence J. et al reported that; with ethanol injection adequate response could be achieved after one or two injections, while, in the case of bleomycin the average number of injections are around 3 to 5 sessions. [5] In this study, the average number of sessions was 3.5 ±0.5.

CONCLUSION

Intralesional bleomycin injection is a safe and effective modality for treating lymphatic malformations. The complications encounteredwere mild and manageable. There is no evidence of associated systemic manifestations in our series.

Abbreviarions: **LM:** Lymphatic malformations.

REFERENCES

1. Zhou Q, Zheng JW, Mai HM, et al. Treatment guidelines oflymphatic malformations of the head and neck. Oral Oncology. 2011;47:1105-9.
2. Legiehn GM, Heran MK. Venous malformations: classification, development, diagnosis, and interventional radiologic management. Radiol Clin North Am. 2008;46(3):545-97.
3. Spence J, Krings T, TerBrugge KG, Agid R. Percutaneous treatment of facial venous malformations: a matched comparison of alcohol and bleomycin sclerotherapy. Head Neck. 2011;33(1):125-30.
4. Mohan AT, Adams S, Adams K, Hudson DA. Intralesional bleomycin injection in management of low flow vascular malformations in children. J Plast Surg Hand Surg. 2015;49(2):116-20.
5. Sainsbury DC, Kessell G, Fall AJ, Hampton FJ, Guhan A, Muir T. Intralesional Bleomycin injection treatment for vascular birthmarks: a 5-year experience at a single United Kingdom unit. PlastReconstr Surg. 2011;127(5):2031-44.
6. Arneja JS, Gosain AK. Vascular malformations. PlastReconstr Surg. 2008;121(4):195e-206e.
7. Lee HJ, Kim TW, Kim JM et al. Percutaneous sclerotherapy using bleomycin for the treatment of vascular malformations. Int J Dermatol. 2017;56(11):1186-91.