ORIGINAL ARTICLE

THE EXPERIENCE OF INTRALESIONAL BLEOMYCIN FOR ORBITAL VASCULAR ANOMALIES

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Background: Orbital vascular anomalies are congenital and pose a challenge. They require various treatment modalities which are often unsuccessful. The use of intralesional Bleomycin has gained popularity in recent times as a scar less procedure when other treatment modalities are not effective. **Purpose:** To share the experience of using intra lesional Bleomycin in orbital vascular anomalies in a Tertiary care hospital. **Methods:** This quasi-experimental study was carried out at Layton Rahmatullah Benevolent Trust (LRBT) Teaching Tertiary care hospital, Karachi from 1st June to 31st December 2018. It included fifteen patients of various orbital vascular anomalies treated with injection of intra lesional sclerosing (Bleomycin) agent. Patients were given multiple injections and the effects of sclerosing agent on orbital vascular anomalies were observed. **Results:** Results were excellent in terms of regression of vascular anomalies. **Conclusion:** Intralesional sclerosing agent (Bleomycin) has an outstanding role in vascular tumour.

Keywords: Bleomycin; Orbital vascular malformation; Capillary haemangioma; Lymphangioma; Orbital varices

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INTRODUCTION

Vascular malformations are congenital anomalies of the vascular system which are fairly common in the younger age group and depending upon their size, they are responsible for cosmetic and functional handicap. There are two types of vascular malformations: slow-flow and fast-flow. Venous or lymphatic malformations are slow flow, arterial and arteriovenous malformations are fast flow. All combinations can present. Childhood vascular tumours have different courses and different prognoses.[1] Most of these orbital vascular anomalies are benign, secluded, or confined; some are locally aggressive and recur after excision. A small number are low-grade malignant lesions with a risk of multi vessel extension, metastasis, and sometimes a fatal outcome. Imaging via magnetic resonance imaging (MRI) has helped towards the non-invasive, non-irradiating exploration and provides information about the extent of the lesions.[2]

Surgically excising the vascular anomalies completely from the orbit poses a danger of iatrogenic damage to the important surrounding structures owing to the infiltrative nature of the lesions. Incomplete excision is associated with the possibility of recurrence. Hence, nonsurgical techniques such as intralesional sclerosing agents have been used as alternative or adjunct therapies.[3]

Well known as a cytotoxic antitumor agent, Bleomycin induces DNA degradation and has a specific sclerosing consequence on vascular endothelium, which has a therapeutic use in the management of haemangiomas and vascular malformation with a significant response rate of 79–88%, obviating the requirement for invasive primary surgery or systemic treatment.[4]

Isolated as a copper containing glycol-oligopeptide antibiotic obtained from the culture medium of streptomyces verticullust; Bleomycin, was found to be an anticancer agent and is used commonly.[5–7] Latest application of Bleomycin A5 was used in recent years for treating haemangioma.[8–10]

The present study was carried out with the aim to share the experience of using intralesional Bleomycin in regressing the orbital vascular anomalies.

MATERIAL AND METHODS

This study was conducted at Layton Rahmatullah Benevolent Trust Teaching Tertiary Care hospital, Karachi, from 1st June–31st December 2018. This study included 15 patients having orbital vascular anomalies with ages ranging from 6 months to 18 years. Inclusion and exclusion criteria are shown in table-1. Procedure was described and consent was obtained from all the patients. A proforma was used to record information. Patients were allotted a group depending upon the anomaly they possessed; i.e., Group A comprised of 5 patients having orbital capillary haemangioma, Group B with 5 patients having lymphangioma and Group C having 5 patients with orbital varices. Patients were enquired especially about their previous photographs, history of steroid use, lung ailment and treatment with Bleomycin for any other pathology. Best Corrected Visual Acuity (BCVA) was recorded after refraction and retinoscopy was performed. The diagnoses of the

aforementioned anomalies were made by clinical examination; however, the presence of a large lesion warranted a CT scan to assess the extent of the lesion. A vial containing 15 units of Bleomycin was diluted with normal saline and a local anaesthetic agent. Following a multi puncture technique, Bleomycin was injected into the lesion. No additional anaesthesia was required for ages 12 and older. Children up to 12 years were injected under general anaesthesia. Smaller lesions required one or two punctures, whereas larger lesions required more punctures. The amount injected depended upon the size and the extent of the lesion and repeated monthly for four months and followed up for 6 months and the results were analysed on a case-by-case basis. Improvement was evaluated by the reduction in dimensions, colour, swelling, cosmetic manifestation, patient's view and was graded as: 0 – No improvement, 1 – Partial improvement and 2 – Complete resolution.

Data analysis was done on statistical package for social services (SPSS) 22.0. Approval was obtained from the institution's Ethical Review Committee.

RESULTS

Bleomycin A5 has a significant effect on orbital vascular anomalies in terms of reduction in size and cosmetic appearance. All 15 patients of this study have improvement to a variable extent. Eleven (73.4%) patients had complete resolution of disease, while four patients (26.6%) showed partial improvement despite receiving all four injections. (Figure-1, 2) Observed results given in table-2.

Table-1: Inclusion/ Exclusion criteria

Inclusion Criteria	Exclusion Criteria
6 months – 18 years age	Old age
Vascular anomalies	Previously treated with steroids
	Previous history of lung disease

Table-2: Results after Intralesional Bleomycin injection

Groups	Grade 0	Grade 1	Grade 2
Group A	0	1	4 (80%)
Group B	0	2	3 (60%)
Group C	0	1	4 (80%)

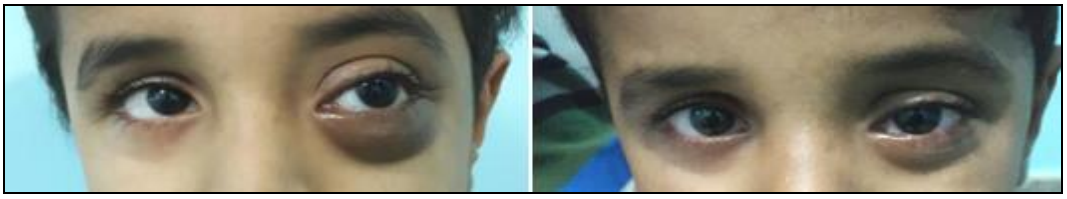

Figure-1: At presentation and post Bleomycin injection

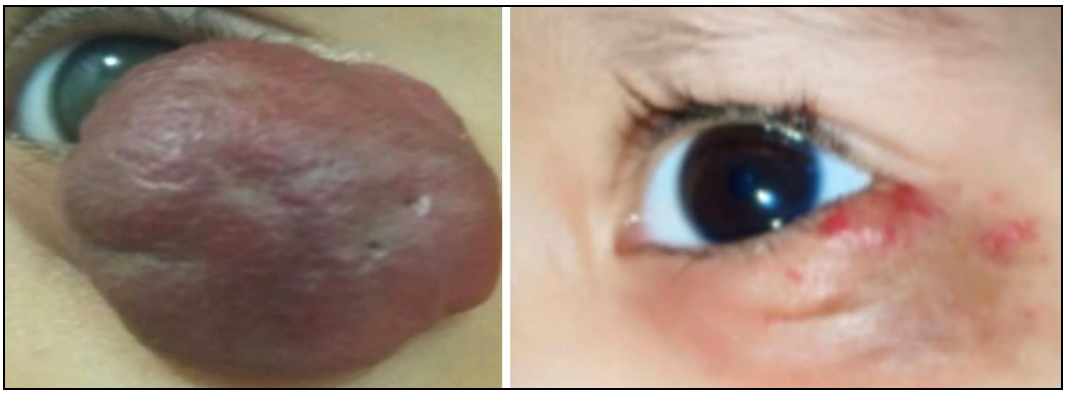

Figure-2: Pre and post Bleomycin injection in case of capillary haemangioma

DISCUSSION

Due to the complex, infiltrative nature and ability to surround vital orbital structures, orbital vascular anomalies are a therapeutic challenge when it comes to their treatment.[11] Intralesional sclerotherapy offers a better adjunct or first line treatment as compared to the surgical intervention which has the potential disadvantage of incomplete excision and collateral iatrogenic damage to the surrounding functional tissues and neurovascular bundles.[12] Previously, the use of sclerosing agents in the orbit has raised concerns with regards to the subsequent pressure effect in the orbit owing to the injection volume and inflammation causing oedema.[13] Intralesional Bleomycin is better tolerated in terms of post injection inflammation and reaction and has proven

to be a valuable treatment of orbital vascular anomalies with the additional benefit of easy availability, better efficacy and minimal side effects. Despite no reported major systemic side effects, sparse literature is available as compared to the other sclerosing agents.[14,15]

The drug Bleomycin is injected in a radial pattern and dosage given according to the age of the patient and size of the lesion. The amount of Bleomycin A5 is usually less than 0.5 mg when the baby is upto 3 month, less than 1.5 mg till the age of 6 months, less than 2 mg before 1 year old and less than 2.5 mg up to 2 years old. The interval of injection was 3–4 weeks with total times less than 7 times during one therapeutic period. Another regime starts after 3 months if further treatment is necessary.[16]

Intralesional/ percutaneous bleomycin injections are generally safe and effective to use in the treatment of small to medium sized vascular malformations. For larger lesions (>4 cm) the treatment is more complex and comprises of a combination of long-term sclerotherapy and surgical procedures over several years.[17] However, systemic use of Bleomycin treatment regimen could result in a potentially serious complication of pulmonary fibrosis.[18]

After intralesional administration, Bleomycin is rapidly absorbed and achieves maximum plasma concentration within a span of 30–60 minutes, distributing all the way through the body with an average volume of distribution of 17.5 L/ m^2 in patients receiving a 15 units/ m^2 IV bolus dose for other pathologies. Bleomycin hydrolase, a systolic cysteine proteinase enzyme which inactivates Bleomycin is extensively distributed within the normal tissues except skin and lungs; which are the targets of Bleomycin toxicity. Since, toxicity of skin is a relatively late complication; developing in the 2^{nd} and 3^{rd} week of treatment, attributed to a cumulative dose of 150–200 units, bleomycin is contraindicated in patients with a known hypersensitivity. It should be stored between 2–8 degrees Celsius and sheltered from light.[16]

Pulmonary fibrosis occurs at a cumulative systemic dose above 400 mg and is dose dependent.[19] Bleomycin, an antineoplastic antibiotic, causes single or double strand DNA breaks and inhibition of DNA and RNA synthesis resulting in endothelial cell detachment with inflammation resulting in fibrosis and involution as well as induction of tumour necrosis factor and apoptosis in rapidly dividing cells.[17,20] In 1977, Yura and colleagues used bleomycin for the first time in the treatment of lymphangiomas.[21] The recommended Bleomycin injection dose is 0.25–0.5 IU/ kg body weight repeated weekly or twice weekly,[22] whereas, in this study the Bleomycin dose used was 0.4–0.5 IU/ Kg body weight, repeated monthly over a period of four months. Conrad Pienaar and his colleagues treated haemangioma with a standard injection of bleomycin of 0.3–0.6 mg/kg per injection. 73% patients had a response rate greater than 75% reduction in size of the haemangioma. Only bleomycin A5 injected in the local site, no other drugs were used.[11] Gooding and Meyer's retrospective study showed significant regression and marked clinical improvement with any ocular or systemic side effects.[17]

Paramivasan and colleagues did a retrospective study of 22 cases of orbital lymphangiomas, of which 16 were treated with bleomycin injection. The follow up period was 6 weeks to 6 months and they reported more than 80% reduction in the volume in 57% cases and 50–79% reduction in the remaining 43%. No systemic adverse effects were observed.[23] In this study, we treated lymphangiomas along with capillary haemangiomas and orbital varices for a follow up period of six months after the last injection.

In our study, we found 73.4% patients had complete resolution of the vascular anomaly following bleomycin injection, while 26.6% patients showed partial improvement over a follow up period of six months. (Figure-1, 2)

Therefore, intralesional bleomycin can be recommended as a first line therapy for orbital vascular anomalies. Although this is a small-scale study, larger scale trials are required to establish this further.

CONCLUSION

There are several ways of treating orbital vascular anomalies, including surgical intervention, but intralesional Bleomycin by far is less traumatic, inexpensive and comparatively easy technique of administration. Therefore, this study recommends intralesional Bleomycin as a first line treatment for orbital vascular anomalies.

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AUTHORS' CONTRIBUTION

ZK: Primary surgeon, Manuscript writer. QQ: Data acquisition, Manuscript writer. MTHK: Statistical help, post interventional management

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