

RESULTS IN THE TREATMENT OF CHILDREN'S FACE AND NECK HEMANGIOMAS AND VASCULAR MALFORMATIONS - WITH INTRALESIONAL OR PERILESIONAL BLEOMYCIN INJECTION

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Abstract

Bleomycin, a polypeptidic antineoplastic antibiotic, was introduced in the treatment of vascular anomalies as sclerosant agent if injected intralesionally or perilesionally. The study was performed between 2008-2012 on a group of 44 children with various vascular anomalies of the face and neck, age ranging from 21 days to 15 years old, who were subjected to local bleomycin injection. For an accurate pursuance and estimation of the efficacy of the treatment, we used the classification of vascular anomalies suggested by Mulliken and Glowacki in 1982 which allowed us a quick diagnosis. Excellent results allowed the usage of bleomycin on a large scale in the local treatment of vascular anomalies located on the child's face and neck. There were no major side effects or complications by intralesional or perilesional bleomycin administration.

Rezumat

Bleomicina, antibiotic polipeptidic antineoplazic, a fost introdusă în tratamentul anomaliilor vasculare, fiind folosită ca agent sclerozant dacă este injectată intralezional sau perilezional. Studiul a fost efectuat în perioada 2008-2012, asupra unui grup de 44 de copii cu diferite anomalii vasculare, vârsta cuprinsă între 21 de zile și 15 ani, la care s-a practicat injectarea locală cu bleomicină. Pentru o încadrare corectă și estimarea eficacității tratamentului s-a folosit clasificarea anomaliilor vasculare propusă în 1982 de către Mulliken și Glowacki, care ne-a permis un diagnostic rapid. Rezultatele foarte bune permit folosirea pe scară largă a bleomicinei în tratamentul local al anomaliilor vasculare, cu localizare la nivelul feței și gâtului la copil. Nu au fost înregistrate efecte secundare sau complicații majore prin administrarea intralezională/perilezională de bleomicină.

Keywords: haemangiomas, bleomycin, sclerotherapy

Introduction

This study represents an update of the treatment of haemangiomas and vascular malformations through a particular procedure: sclerotherapy with intralesional and perilesional bleomycin injection. The technique of intralesional injection is not new, but the injected substance seems to have real advantages.

For a better estimation of the chosen type of treatment, the diagnosis must be as accurate and as possible. It is important to find a simple clinical classification suitable to the varied aspect of vascular anomalies and, at the same time, corresponding to the anatomopathological forms.

We used the classification done by the International Society for the Study of Vascular Anomalies in Rome in 1996. This classification is based on the studies of two American researchers, Dr. Mulliken and Dr. Glowacki [8]. In this study we used the

following classification: the lesions with abnormal vascular components generically called vascular anomalies are divided in: haemangiomas or benign vascular tumours which represent a benign neoplastic proliferation of endothelial cells [1]; vascular malformations, which are errors of the vascular morphogenesis; syndromes associated with vascular anomalies.

The criteria to differentiate between haemangiomas and vascular malformations can be summed up as follows:

- Generally haemangiomas are not present at birth; most of them appear during the first month of life, while vascular malformations are visible within a few hours from birth, though sometimes they remain invisible till later on, in life.
- It is well known the fact that, unlike vascular malformations that grow invading the neighbouring tissue and don't involute and cannot be completely

eradicated, haemangiomas involute spontaneously, leaving residual scarring. This classification does not include the malignant lesions whose starting point is a component of the vascular system.

This study concerning the results of sclerotherapy using intralesional injections does not apply to vascular lesions associated with syndromes or related to chronic liver disorders, drug administration or hormonal states.

We start the treatment when the involution of the vascular anomaly, especially of haemangiomas, is complete, even if that takes years.

The present study uses intralesional bleomycin injection in the treatment of vascular anomalies. bleomycin is a polypeptidic antibiotic produced by means of culture fermentation from *Streptomyces verticillus*, known and used in medical practice as antineoplastic agent. The mechanism of action is the inhibition of DNA replication of vascular cells and RNA protein synthesis, and the break of simple and double DNA molecule in vascular cells. The medical literature presents teratogenic, mutagenic and even carcinogenic risks. bleomycin is used in various ways in the treatment of germ cell tumours of children, carcinomas of head and neck, lymphomas, osteogenic sarcomas, skin cancers, genital cancers and namely, testicular cancer or squamous cell cancers of penis and vulva [6]. The dosage used in oncology as antineoplastic implies numerous adverse effects: partial alopecia, hyperpigmentations, rashes, nail changes, stomatitis, nausea, vomiting, fever, anaphylactoid hypersensitivity, interstitial pneumonias (in 10% of cases), and pulmonary chronic fibrosis in approximately 1% of cases. Pulmonary fibrosis can appear in the case of high therapeutic doses (over 400-500 U), which is the maximum dose allowed for patients in oncological practice [14]. Lung toxicity rises in patients treated with bleomycin, suffering from: either acute or chronic pulmonary affections, patients exposed to high doses of oxygen during anaesthesia, patients receiving drug in bolus, patients suffering from kidney failure and patients who undergo radiation therapy. The dose used for local therapy does not exceed 1-2 mg/kgbw/injection, considering that the absorption in the systemic circulation from the local injection is even in cases of capillary, venous or lymphatic vascular malformations. In case of arterial vascular malformations the sclerotherapy can be done after embolization [5].

The treatment with intralesional bleomycin injections can be started within the first 2-3 weeks of life. It can be used as the only treatment for vascular anomalies or in combination with other therapies that can stop the proliferation of these vascular lesions, like cortisone, interferon or propranolol [9], although it is well known that most

of haemangiomas regress spontaneously during the first years of life, which determine us to postpone any treatment. There are no objective parameters to subject the rapid evolution and extension of these lesions [7]. When these rapidly enlarging lesions are located in particular areas of the body and are difficult to be surgically removed, related complications are present, it is recommended to start the sclerotherapy associated with a systemic complementary medication [11, 12]. The indications for sclerotherapy may be synthesized as follows:

- Deep massive vascular anomalies of head and neck inoperable because of the large surface involved.
- Lesions with long time ulceration and secondary anaemia.
- Vascular anomalies with particular locations involving structures like: ear canal, nose (the so-called Cyrano deformity, collumela, and nares), eyelids, lips, tongue, pharynx, larynx or the oral cavity. These locations are at risk as they may produce respiratory, auditory, visual or olfactory dysfunctions.

The intralesional injection is a relatively simple procedure from a technical point of view, but it is necessary to be performed under general anaesthesia, especially in infants and small children. The duration of intervention ranges between 3 and 10 minutes (average 7 minutes), depending on the involved area of the lesion and the need of compression if it is bleeding. Another strong argument in favour of general anaesthesia is that the procedure involves sensitive locations (eyelids, nose, digits, lips, tongue) necessitating a certain precision and attention, in order to avoid damaging the neighbouring organs and tissue. The action period of the anaesthetic is quite short and does not need any further precautions besides those taken in case of similar interventions. Local anaesthesia can be used in older children who cooperate better. Local anaesthesia does not increase the bleeding time through vasodilatation, therefore it doesn't produce important bleeding. It can be noticed that, despite the first impression when seeing a vascular anomaly, the bleeding is minimal and it stops rapidly even if the injection is performed into the lesion or nearby, if there is no coagulation anomaly [10].

The necessary lab investigations for this procedure are: haemoglobin level, thrombocytes and coagulogram. Echography, computed tomography and magnetic resonance imaging (MRI) were used for huge lesions in order to assess precise by the extension of the anomaly in the neighbouring organs [2].

Bleomycin is available under the form of lyophilisate - Bleocin® - for injectable solution

containing 15 mg of bleomycin clorhydrate. The main component is Bleomicina A2 in proportion of 55-70% under the form of a yellowish white powder. It is soluble in water and ethanol. Before the administration, bleomycin injection it is mixed with physiological serum. The total volume of the mixed solution depends on the dosage and on the anatomic location of the area where it is injected [13]. When injected into haemangiomas in locations with little or absent subcutaneous tissue or in locations where the tissue does allow the insertion of a large quantity of solution (hardly expandable tissue like nose, ear pavilion, eyelids), a 15 mg vial was dissolved in 7.5 mL of physiological serum in order to obtain a 2 mg/mL concentration. 1 mg bleomycin / 1 mL physiological serum was injected into the lips, where insertion of large quantities of solution would have created tumefaction causing child discomfort, while eating or speaking. Bleomycin can be used associated with Dexamethasone in order to diminish the inflammatory and allergic regional reaction. In this case, the solution for injection is prepared by mixing 1 vial bleomycin with 6 mL physiological serum, 2 mL Dexamethasone (a 2 mL vial containing 8 mg) and 2 mL Lidocaine (Xiline 2%). Depending on the size of the lesion, we injected between 1 and 4 mL of solution in the above mentioned dilutions. The administration was performed surrounding the haemangioma. The procedure was repeated at intervals of 2-5 days, depending on the local reaction and the size of the vascular lesion assessed at the initial evaluation. The maximum dose administrated was 1 mg/kgbw/injection which did not exceed the total dose of 50-100 mg (dose that causes adverse reactions in local

injections, according to the medical literature) [4]. After injection, the bleeding had to be controlled through compression for several minutes, but compressive bandage were avoided because of hyperpigmentations which appear in compressed surrounding areas and even in areas where adhesive bandages were used.

Materials and Methods

Between 2008– 2012 “Marie S. Curie” Emergency Children Hospital–Department of Paediatric Surgery, 94 children with vascular anomalies of the face and neck were hospitalized, 44 of them underwent the treatment with intralesional/perilesional bleomycin injection. The other 50 children were operated by total or partial excision of the vascular lesions.

This type of local treatment with intralesional bleomycin was applied under the above mentioned terms with the parents' agreement by using dosage adapted to children's age and weight at different time intervals depending on the treatment reaction and the tolerance during the treatment. The youngest patient was 3 weeks old, but the treatment can be applied at any age during childhood as described: 0-1 month (4 cases); 1-12 months (12 cases); 1-3 years (16 cases); 3-7 years (8 cases); 7-15 years (4 cases).

In 78% of cases, the vascular lesions were single and 22% were multiple.

From 94 cases of haemangiomas localized in face and neck, 44 cases were perilesionally/ intralesionally injected with bleomycin as described in Table I. In 20% of the cases, the children needed more than 5 subsequent interventions.

Table I
Cases of haemangiomas treated with bleomycin

Localization	Total number of haemangiomas localized in face and neck	Number of cases injected with bleomycin
Tongue	4	4
Lips	20	8
Eyelids	10	6
External ear	2	2
Cervical region	12	6
Nose	10	6
Other regions of the face (cheek, zygomatic region, frontal region, eyebrows, etc.)	36	12
Total	94	44

Results and Discussion

The results are encouraging considering the relatively simple procedure and its almost insignificant adverse reactions, which allowed us to use bleomycin in cases of haemangiomas or vascular malformations with special location (face, neck) in children.

The treatments were applied in operating rooms. None of the patients bled or suffered from local infections.

The adverse reactions caused by injections were registered. Within a few hours from injection, in 51% of the cases, the children experienced pain which was treated with non-steroid analgesics. Oedema appeared in 98% of the cases, but it wasn't

intense and remitted after 24-36 hours at most. Oedema was accompanied by localized hyperaemia of the injected region and even of the neighbouring tissue within 4-5 millimetre distances, circumscribing the oedema. Hyperaemia disappeared at the same time with the oedema.

Fever (38-38.5°C) was registered in 14% of children. It was caused by the local insertion of the sclerosing substance. Fever appeared within an hour after procedure and it was easily treated with antithermic drugs. Only in one case, of a 10 months infant, whose cheek haemangioma was injected with bleomycin, fever (38°C) appear and it was followed by urticarial placards at first on the face and then on limbs and body which caused the interruption of the treatment. This was the only allergic reaction observed in the studied group. In 11% of the cases, regardless the fact that the injection was done into the haemangioma or nearby, small ulcerations appeared and they were rapidly covered with a crust.

A particular frequent lesion, unrelated to the puncture place, was the development of squamous metaplasia on the injected haemangioma. In 61% of the cases this hyperkeratinisation remained visible for 3-12 days. The squamous lesions didn't appear with increased intensity in the same child after subsequent injections, but their presence after 7 days made us enhance the interval between injections until their disappearance.

Shortly after the first or second injection all haemangiomas lost their intense initial color. Subsequently, a month after the interruption of the treatment, we could notice during examination the limit of regions of tegmental and mucous atrophy on the vascular anomaly in 45% of the cases. The atrophy took two forms: septa and easy retractable fibrous tissue especially on lips mucous or small tegmental placards sometimes temporarily hyperpigmented. Hyperpigmentation was encountered in 38% of the treated patients and it was temporary, disappearing after a few weeks.

Concerning the aspect of the lesion, we registered the following clinical results:

- significant reduction: 58% of cases;
- complete disappearance: 34% of cases;
- no improvement (with stationary or evolving lesions): 8% of cases.

We obtained better results after using intralesional bleomycin injection on haemangiomas – 85% with excellent results when compared to administration of the procedure for vascular anomalies.

One of the most difficult cases was one of a 21 days child hospitalized for ulcerated giant haemangioma on the cheek which appeared at birth as a small teleangiectatic formation. The rapid extension of the lesion and the emergence in a short time of the ulceration, made us start the bleomycin treatment.

After 8 injections at one week interval, the result was spectacular (Figure 1).

In this case, we managed to control the effusive growing of the haemangioma and give the surgeon a lesion relatively easy to correct [3].



Figure 1.

Before treatment (left). After 8 injections with bleomycin (right)

Another case is a periocular haemangioma, which needed injections with bleomycin intra and perilesional. After 6 injections, under general anaesthesia, we obtained a positive result (Figure 2).

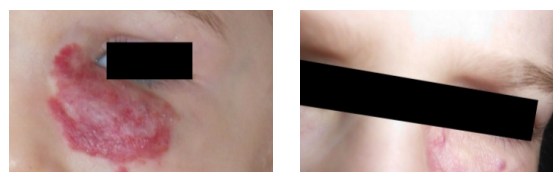


Figure 2.

Before treatment (left). After 6 injections with bleomycin (right)

Lip haemangiomas responded very well to the treatment with intralesional bleomycin injection. This is the case of an 8 year old girl whose upper lip started to look almost normal after 6 injections (Figure 3) [3].

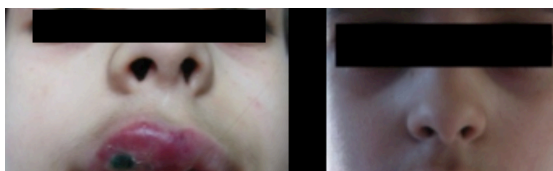


Figure 3.

Before treatment (left). After 6 injections with bleomycin (right)

Conclusions

The good results obtained allow us to recommend the application of this treatment before deciding to operate some vascular anomalies with particular localisation which makes them difficult to approach.

The gathered experience allowed us to treat the effusive growing of vascular anomalies which had, in their evolution, the tendency towards exuberant development.

In many cases we have successfully prepared the way for subsequent plastic and correcting surgeries.

We point out that the treatment with intralesionally injected bleomycin, under the conditions mentioned in the study, proved to be safe; no adverse reaction usually described for doses in oncology was registered. The recorded post injection reactions were harmless temporary and easily treatable. Nevertheless, the pursuance in time of a large number of patients and the gathered experience made us more cautious when choosing and applying any treatment for vascular anomalies.

References

1. Smit D.P., David M., Intralesional bleomycin for the treatment of periocular capillary hemangiomas. *Indian Journal of ophthalmology*, 2012; 60: 326-328.
2. Hassan Y., Osman A.K., Altyeb A., Noninvasive management of hemangioma and vascular malformation using intralesional bleomycin injection. *Ann. Plast. Surg.*, 2013; 70(1): 70-73.
3. Ionescu S., Andrei B., Secheli I., Secheli M., Ivanov M., Treatment of hemangiomas and vascular malformations with intralesional bleomycin. 4th World Congress of Pediatric Surgery Children's Surgery with Competence & Heart, October 13th – 16th, 2013; Berlin – Germany.
4. Kullendorf C., Efficacy of Bleomycin treatment for symptomatic hemangiomas in children. *Ped. Surg. Int.*, 1997; 12: 526-528.
5. Mabeta P., Pepper M., Hemangiomas - current therapeutic strategies. *Int. J. Dev. Biol.*, 2011; 55: 431-437.
6. Mathur N.N., Rana I., Bothra R., Dhawan R., Kathuria G., Pradhan T., Bleomycin sclerotherapy in congenital lymphatic and vascular malformations of head and neck. *Int. J. Pediatr. Otorhinolaryngol.*, 2005; 69: 75-80.
7. Muir T., Kirsten M., Fourie P., Dippenaar N., Ionescu Go., Intralesional bleomycin injection (IBI) for hemangiomas and congenital vascular malformations. *J. Pediatr. Surg.*, 2006; 39: 1735-1736.
8. Mulliken J.B., Glowacki J., Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast. Reconstr. Surg.*, 1982; 69: 412-420.
9. Pandey A., Gangopadhyay A., Upadhyay Vd., Evaluation and management of infantile hemangioma: An overview. *Ostomy Wound Manag.*, 2008; 54: 16-18.
10. Pienaar C., Graham R., Geldenhuys S., Hudson D.A., Intralesional bleomycin for the treatment of hemangiomas. *Plast. Reconstr. Surg.*, 2006; 117: 221-226.
11. Richard J.A., Infantile Hemangioma, 2009; eMedicine.
12. Sarihan H., Mocan H., Yildiz K., Abes M., Akyazici R., A new treatment with Bleomycin for complicated cutaneous hemangioma in children. *Eur. J. Ped. Surg.*, 1997; 7: 158-162.
13. Shapour O., Nosrat N., Niloofar A., Ahmad M., Role of Intralesional Bleomycin in the Treatment of Complicated Hemangiomas: Prospective Clinical Study. *Dermatol. Surg.*, 2005; 31: 499-501.
14. Vibhu M., Masarat J., Infantile hemangioma: An update. *IJDVL*, 2010; 76(5): 469-475.