Treatment of viral warts with intralesional bleomycin

A verruga viral representa uma das dermatoses mais prevalentes. O quadro clínico varia de lesão única com uma spontânea até múltiplas lesões recalcitrantes. O sulfato de bleomicina é uma droga de ação citotóxica, aprovada para o tratamento quimioterápico de algumas malignidades. Há mais de 45 anos existem trabalhos demonstrando sua utilidade na dermatologia, em especial na terapia intralesional para verrugas virais, que constituem excelente opção para as lesões em topografias de difícil manejo e para os casos não responsivos a outras abordagens.

Palavras-chave: Bleomicina; Tratamento farmacológico; Verruga viral

INTRODUCTION

Bleomycin was originally isolated from the fungus Streptomyces verticillus, in 1962, by Umezawa et al.\(^1\) This glycopeptide has antibacterial and antiviral effects, however, it is very useful because of its cytotoxic effect. It was approved by the Food and Drug Administration (FDA) for systemic treatment of testicular carcinoma, malignant pleural effusion, Hodgkin and non-Hodgkin lymphoma. It was approved as adjuvant chemotherapy for the treatment of some advanced form of cutaneous squamous cell carcinoma.\(^2\) Due to its low transepidermal absorption, a very high dose is required to achieve minimum tissue concentration when applied topically.\(^3\) Therefore, intralesional injection becomes an option for

Pharmacodynamics

Knowing its low absorption when administered orally, intravenous, intramuscular or subcutaneous administration should be used in cases of systemic treatment, according to the approach protocol.\(^3\)

ABSTRACT

Viral warts are one of the most prevalent dermatoses. The clinical picture varies from a single lesion with spontaneous cure to multiple recalcitrant lesions. Bleomycin sulfate is a cytotoxic action drug approved for the chemotherapeutic treatment of some malignancies. There are a number of studies that have been carried out during the last 45 years demonstrating its usefulness in dermatology, especially in intralesional therapy for viral warts, meaning it is an excellent option for lesions in difficult-to-handle topographies and for cases that do not respond to other approaches.

Keywords: Bleomycin; Drug therapy; Viral wart

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the treatment of localized lesions. It is considered that systemic absorption is minimal after one intralesional injection.7,8

James et al.9 dosed the serum level of bleomycin in seven patients with palmar viral warts after injection of one unit (U) of the drug. Serum concentration ranged from 7.5 to 113.5ng/ml and from 4.9 to 34.8ng/ml after 45 and 120 minutes, respectively.

It is mainly excreted through the kidneys, but liver participation is suggested.3,10 There is also enzymatic destruction with bleomycin hydrolase, enzyme found in many tissues, in varying concentrations.3

Mechanism of action
It acts mainly via cleavage of the DNA strand. In the presence of oxygen, Fe2+ and a reducing agent, bleomycin transfers electrons from Fe3+ to oxygen, generating reactive oxygen species. The free radical causes oxidative damage to the nucleotides, cleaving the DNA strand.9 There is also degradation of cellular RNA.11 Another mechanism of action related to a good therapeutic response in viral warts is endothelial damage.11 Direct effect of bleomycin on human papillomavirus (HPV) was not described.

Because it is a hydrophilic substance, its permeability through the cell membrane is low. Mizuno e Ishida12 demonstrated that the association of bleomycin with lidocaine, procaine, tetracaine, dibucaine, butacaine or ethanol generates an increased cytotoxic effect. These substances would cause a disorganization of the cell membrane and, therefore, increased transmembrane permeability.3,12

Pharmaceutical form
The preparation commercially available is bleomycin sulfate, lyophilized powder, in vial/ampoule with 15U.3,4

Viral warts
Cutaneous viral warts are a common, benign skin infection, caused by HPV, that most frequently affects hands and feet (Figure 1).13,14 The presentation and severity can vary from a single lesion with spontaneous resolution to multiple, chronic lesions. They affect any age group, with a prevalence ranging from 5% to 30% in children and young adults.13-15

Immunosuppressed individuals are highly susceptible, with long standing lesions and reduced response to treatment.13,15 Besides aesthetic and functional limitations, we should bear in mind the association between HPV and cutaneous squamous cell carcinoma.15 Therefore, it is important to biopsy chronic verrucous lesions in adults, since they can represent malignant epithelial neoplasms.

Cryotherapy, salicylic acid, lactic acid, glutaraldehyde, imiquimod, electrocautery, surgical excision, curettage, podophyllotoxin, cantharidin, 5-fluorouracil (topical or intralesional), immunotherapy, photodynamic therapy and pulsed dye laser are described as therapeutic options.3,10,14

The site, size, number of lesions and previous treatment failures will influence the choice of therapeutic approach.

Intralesional bleomycin for the treatment of viral warts
The first description of intralesional bleomycin for the treatment of viral warts was in the 1970s, and since then many studies have confirmed its efficacy and safety. For many authors, this is an excellent therapeutic option for difficult-to-approach sites, particularly the periungual region (Figures 2 and 3), and for recalcitrant lesions, even in immunosuppressed individuals.3,8,9,11,13,14,16,17

Dhar et al.18 assessed 73 patients between 5 and 50 years of age, with a total of 155 warts, comparing cryotherapy with intralesional bleomycin. The cure rate in the bleomycin group was of 94.9%; in the group treated with cryotherapy, 76.5%.

In a similar study, Adalatkhal et al.19 demonstrated cure in 86% and 68% of the cases treated with bleomycin and cryotherapy, respectively. Rossi et al.20 demonstrated a cure rate of 82%, 2.5-fold higher than in the placebo group.

Besides common and palmoplantar warts, there are studies showing efficacy for the treatment of anogenital warts, with a cure rate of up to 70%.21

Since intralesional bleomycin is a modality considered to be off-label, there is no standardized dilution. Most authors describe the use of this drug in varying concentrations, from 1 to 1.5U/ml:

- 15ml saline 0.9% for 15U bleomycin = 1U/ml.2
- 5ml distilled water for 15U bleomycin. Mix 1/3 of this solution with 2/3 2% lidocaine = 1U/ml.18,22
- 4 ml saline 0.9% + 6 ml 2% lidocaine for 15U bleomycin = 1.5U/ml.21

The needle should be inserted at the base of the lesion and the injection continued until the local blanching is achieved.18,21 This is an important sign that the medication was correctly injected.3

Most articles mention that the ideal dose should range between 0.1 and 0.3U/lesion, and 3U is the maximum dose recommended per treatment. Usually, 2 or 3 treatments are required, every 3 or 4 weeks.3,18,21,23
For lesions on the hands and/or feet, in the first week after the procedure, the formation of hematic and darkened crusts is expected. This is due to the absolute reduction in blood flow, which results in necrosis and subsequent disappearance of the lesion (Figure 4). In general, there is resolution in 2 to 4 weeks. Facial warts regress gradually and the lesions disappear without crust formation. Blood flow is probably reduced after injection; however, it is not completely blocked due to the rich vasculature of this area. Induction of endothelial apoptosis and direct keratinocyte injury can result in wart regression without necrosis or eschar.

Application of a drop of bleomycin solution on the surface of the lesion, followed by multiple punctures is an alternative to intralesional therapy that was described as translesional multipuncture. Khalid et al. used this technique in 15 patients, using 0.1 U/ml bleomycin solution and a 27G needle. The dose used ranged between 0.3 and 0.6 ml per treatment. After 4 weeks, another treatment was performed in cases that persisted or recurred. They observed that 46.6%, 73.3% and 86.6% had a good response after 1, 3 and 6 months after the procedure, respectively.

Side effects
Pain is one of the main limiting factors of this treatment, which can last up to 72 hours, with a peak at the time of injection. This would be one of the reasons why some authors use lidocaine as diluent, reducing pain during and immediately after the procedure.
Other common side effects of the intralesional therapy with bleomycin are: erythema, edema, ulceration, hematic crust formation and eschars.12,16

Transient hypopigmentation or hyperpigmentation can occur (particularly in phototype IV, V or VI patients), atrophic or hypertrophic scars and hematomas. Less frequently, Raynaud phenomenon, digit necrosis, ungual dystrophy and loss of the nail were described after injection of periungual warts.2,4,9 Although rare, flagellate dermatitis can also occur with intralesional therapy.3,4

There are no reports of systemic complications with the use of intralesional bleomycin, except for flu-like symptoms, only described in the treatment of hemangiomas or vascular malformations.7,21,25

Options to reduce pain during intralesional injection3,26
Application of topical anesthetic or local injection
Using small diameter needles (27G or 30G)
Substitution of the needle when multiple punctures are necessary
Stretching or pinching adjacent skin
Applying ice or specific vibration devices

Inject slowly
Avoid a large volume by application area

Contraindication
Hypersensitivity or idiosyncratic reaction to the medication, Raynaud phenomenon, peripheral vascular disease, pregnancy (category D) and breastfeeding.3,27

There are no safety studies regarding intralesional use in the pediatric age group.3

CONCLUSION
Despite being described for many years as an effective and safe therapeutic approach for viral warts, intralesional injection of bleomycin remains an off-label option. Studies revealed a high cure rate even in cases refractory to other therapies, in lesions on difficult-to-handle sites and in immunosuppressed patients. Pain is the main limiting factor of this procedure.

We highlight the importance of histopathology in the evaluation of long standing verrucous lesions in adults, because they can represent a squamous cell carcinoma and not only a plain viral wart.

REFERENCES

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