

Therapeutic Profile of Intralesional Bleomycin Injection in the Management of Common Warts: A Systematic Review

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Abstract: *Verruca vulgaris*, the common wart are painless, circumscribed, firm elevated papules with papillomatous ("verrucous") hyperkeratotic surfaces. They most commonly presents singly or in groups on the dorsal aspects of the fingers and hands. Rarely, *verrucae vulgaris* occur on the oral mucosa. They are frequently noted among children, adolescents and predominates in those with a profound degree of immunosuppression, making the cutaneous infection difficult to eliminate. A wide range of therapies currently in use for the treatment common warts show variable rates of success. Intralesional bleomycin administration is an upcoming treatment option for common warts that appears to give promising results.

Keywords: intralesional bleomycin warts, verruca vulgaris, bupivacaine hydrochloride 0.5%, HPV, human papilloma virus, bleomycin injection treatment

1. Introduction

Cutaneous warts remains as the most common manifestation of human papilloma virus infection known to humans and most people experience HPV infections at some point in their life. The varied appearance of the lesions is attributed to the different genotypes and also the difference in environmental and host factors. Patients often seek medical help due to the unsightly appearance of these lesions or the discomfort associated with the lesions. There is still not one treatment modality that is considered to be 100% effective in treating cutaneous warts.

The ideal treatment option must be able to eliminate the lesion completely with minimal chance of reappearance, maintaining skin texture and integrity and also boosting individual's immunity to combat the infection better and confer lifelong immunity. The intralesional bleomycin injection, an anti-neoplastic drug appears to give promising results for common warts due to preferential binding with squamous cells, non-toxic DNA strand break/damage.

Although the administration of bleomycin injection is quite painful and may require administration of local anaesthetics prior to the procedure, it may be readily made accessible even in the periphery centres due to its affordable storage requirements. Also, the sustained efficacy of bleomycin have been proven in the previous studies conducted so far. (9, 19) This systematic review collates the novel and rationale therapeutic management of common warts using intralesional bleomycin injection.

2. Discussion

Bleomycin, a cytotoxic agent belonging to the anti-tumour antibiotic subfamily that was first isolated by Umezawa in 1965 from the soil near a Japanese coal mine, appears to be a upcoming treatment option for common warts. Treatment of verruca vulgaris has been successful with this product. (33) It has now been utilised to treat a variety of cancers,

including lymphoproliferative syndromes, squamous cell carcinoma, and testicular tumours because of its properties such as selectional binding to squamous cells causing DNA strand scission while causing limited damage.

3. Mechanism of Action

Bleomycin induces DNA oxidation by creating metalbleomycin complexes with metal ions, especially iron. These complexes produce reactive oxygen species, causing single-strand and double-strand breaks in DNA between 3'-4' links. The generation of free base propenals, especially thymine, is caused by these strand breaks, which induces cell cycle arrest in the G2 phase. After bleomycin treatment, cytological examination revealed chromosomal abnormalities, fragmentation, chromatid breaks, and translocations.

When the enzyme bleomycin hydrolase, also known as a cysteine proteinase, is present in normal tissues, this is associated with bleomycin resistance. Iron binding and cytotoxicity are reduced as a result of the substitution of a terminal amine with a hydroxyl group by this enzyme. It's been hypothesised that skin and lung tissue have distinct bleomycin sensitivity because of the lesser concentration of the enzyme hydrolase. It has a low myelo-suppressive impact, and the majority of its toxicity appears to occur in the skin and lungs, where concentrations are greater; the effects are typically dose limiting.

4. Metabolism & Toxicity

Because bleomycin is poorly absorbed by the gastrointestinal system, it is administered through the parenteral route. After an intramuscular, subcutaneous, intraperitoneal, or intrapleural injection, bleomycin is quickly absorbed, reaching peak plasma concentrations in approximately 60 minutes. The half-life is affected by a number of factors, including the method of administration, and it varies greatly across people. Because less than 1% of

medicine given intravenously binds to plasma proteins, it has a higher bioavailability than orally supplied drug. Although evidence from studies suggests that bleomycin is removed by first-order rate kinetics, with a mean plasma drug clearance of about 70 mL/min/m², the metabolism of the medication is poorly known. Bleomycin has a high rate of plasma clearance and urine excretion as a result of this.

Bleomycin pulmonary toxicity (BPT) was first documented in the early 1960s as an irreversible side effect of the medication, but rates have lately been modest (about 10%). As a result, thorough toxicology monitoring is required. BPT has the potential to induce severe pulmonary fibrosis. Cumulative dosage, elevated creatinine, advanced age, supplementary oxygen, and a decreased glomerular filtration rate are all risk factors for BPT. Several studies have shown that bleomycin can be used in place of less toxic chemotherapy and immunotherapy drugs in multi-drug regimens to achieve equivalent results. This is especially beneficial for individuals who have several BPT risk factors or who have a low-grade illness that does not need BPT.

Monitoring

Chest imaging methods such as magnetic resonance imaging (MRI), computed tomography (CT), and plain film X-rays are often used throughout treatment to monitor liver enzymes, blood counts, plasma proteins, and electrolytes. In the absence of other diagnostic techniques, imaging alone is an inconclusive way of determining bleomycin pulmonary toxicity. Patients' treatment and monitoring plans frequently include the use of pulmonary function tests, in addition to imaging studies.

Reconstitution:

There are 15U/vial and 30U/vial bleomycin sulphate powders available. It should be stored at 2–8°C. At room temperature, the shelf life is 24 hours, while when refrigerated, the shelf life is 4 weeks. When reconstituted with regular saline rather than distilled water, the shelf life is reported to be longer. It has a difficult time diffusing across cell membranes. By breaking cell membranes, reconstitution in local anaesthetic (lignocaine or bupivacaine) increases penetration.

To prepare the stock solution for intralesional injection at a concentration of 1mg/ml, 15mg vial bleomycin powder is dissolved in 5ml distilled water to prepare 3mg/ml stock solution. One part of the bleomycin stock solution and two parts of 2% lignocaine were mixed in an insulin syringe with 30 G needle to obtain a final bleomycin concentration of 1 mg/ml just before intralesional infiltration. (4)

Treatment Protocol:

Bleomycin is administered intralesionally until blanching of the lesion observed. The amount of bleomycin is limited to 1mg/ml for a single wart when >10 large warts are identified, with a total cumulative injected volume not exceeding 2 ml on a single treatment session. Sterile dressing and non-steroidal anti-inflammatory agents are prescribed for 2–3 days to alleviate post-injection site erythema, swelling, and pain. A black, keratotic eschar is formed at injection site which requires paring after 2 weeks to repeat treatment of residual lesions. (4)

Contraindications:

Although there appear to be no definite contraindications to bleomycin usage at this time, a history of lung illness and renal function testing should be performed prior to delivery. Patients who have smoked in the past are more likely to have lung problems. Patients in this category include the elderly, those with stage IV illness, those who get bolus medication administration rather than continuous infusion, and those who require supplementary oxygen. It is extremely teratogenic and is not utilised in the same way as other anti-neoplastics.

Table 2: Cure Rates of Intralesional Bleomycin Injection For Palmo-Plantar Warts (4)

Reference, year of publication	Treatment schedules/methodology	Cure rate (%)
Shumer and O'Keefe, 1983	IL 1 mg/ml 2 weeks apart and follow up to 12 months	60
Hayes and O'Keefe, 1986	IL 1 U/ml at 0, 3, 6 weeks final assessment at 3 months	76
Bunny et al.1984	0.5 U/ml IL at 0, 3, 6 weeks and assessed at 12 weeks	76
Amer et al.1988	0.1 ml for <5 mm and 0.2 for >5 mm of 1 mg/ml bleomycin warts 2 I/L. injections 2 weeks apart for 8 weeks	47.6
Munn et al.1996	1 U/ml solution dropped on wart surface and pricked multiple times. Repeated monthly till clearance	92
Shelley and Shelley.1991	Two IL injections 1 U/ml 3 weeks apart and followed up to 6 months	92
Soni et al.2011	Two IL injections 2 weeks apart in 1 mg/ml strength.	96.5
Agius et al. 2006	IL 1 U/ml by dermojet 5 weeks apart for 25 weeks	89.9
AlGhamdi and Khurram, 2012	Translesional bleomycin 0.1/ml 4 weeks apart till clearance or development of side effects	86.6
Kruter et al. 2015	IL 3 U/ml 3 weeks apart. Follow up to 6 months	74

I/L: Intralesional

Dose of Bleomycin in various conditions:

- In cancer chemotherapy in high doses (>450 units). Bleomycin is used in cytotoxic chemotherapy combinations, such as ABVD ([adriamycin], doxorubicin, bleomycin, vinblastine, dacarbazine).
- keloids (1.5 IU/ml or 0.1–1 ml/monthly),
- periungual warts (0.1–2 ml/session, monthly, up to 4 injections/wart),
- large hemangiomas and
- venous malformations (0.3–1 mg/kg, up to a maximum of 15 mg/month)

5. Adverse Effects:

Bleomycin pulmonary toxicity, or BPT, is a systemic side effect. Pulmonary fibrosis is a persistent, irreversible illness with a bad prognosis that can be caused by this side effect. Bleomycin administration increases the likelihood of functional alterations in lung endothelial cells, however the specific mechanism of these changes is unknown. Fever, chills, faintness, chest discomfort, and shortness of breath are some of the other side effects. Skin pigmentation changes, itching, hypogeusia, rash, nausea, vomiting, and weight loss are among less significant responses. Some of

these signs and symptoms appear to be linked to a hypersensitive reaction.

Table 3: Cutaneous Side Effects

On parenteral administration	On intradermal administration	
Hyperpigmentation(diffuse, patchy or linear, band like or "flagellate")	Common	Redness
Alopecia,		Swelling
Stomatitis		Pain and burning (subside after 72 hrs).
Nail changes		Hemorrhagic eschar (ecchymosis)
Painful inflammatory nodules on fingers,	Rare side effects	Raynaud's phenomenon,
Warty hyperkeratotic plaques on the knees and elbows,		Narrowing of fingertips,
Digital gangrene,		Restricted nail growth,
Erythema multiforme,		Scarring,
Infiltrated violaceous plaques,		Lymphangitis,
Sclerodermoid changes		Paresthesias and hematoma formation

6. Review of Literature

In 1983, double-blind placebo-controlled study conducted by Shumer and O'Keefe *et al.* treated 151 warts with IL bleomycin and 55 warts with normal saline as placebo. Their study showed a 60% clearance in plantar warts and a 94% clearance in periungual warts (15). Further Aziz-Jaleli *et al.* assessed bleomycin in periungual warts and found 73% clearance (29).

An Indian study by Soni *et al.* showed clearance rate of 96.10% with 2 injections 2 weeks apart at 1mg/ml strength in 2001 (16). Dhar *et al.* used 1mg/ml of bleomycin 3 weeks apart for maximum 4 injections in 39 patients with 87 warts with 94.9% clearance rate and another 68 warts with cryotherapy which showed only 44% clearance (2).

Bunney *et al.* showed only upto 76% clearance with 3-4 sittings and included treatment resistant warts (17). Golchai *et al.* studied IL bleomycin for upto 3 sittings with palmoplantar and periungual warts and found 88.4% clearance. Salk and Douglas *et al.* observed upto 87% clearance with plantar warts (29). Kruter *et al.* gave upto 3mg/ml 3 weeks apart and observed only 74% cure rate (30). Mehta *et al.* showed 84% cure with common warts including periungual warts with 1mg/ml concentrations (4). But with the same concentration of bleomycin, Unniet *al.* got clearance of 93.1% lesions (9).

Hayes and O'Keefe used 0.05% of bleomycin (in more diluted form) in 26 patients with 62 warts where 76% clearance was observed. A more dilute (0.05 percent) concentration of bleomycin was employed by Hayes and O'Keefe and injected into 62 warts on 26 patients, with a cure rate of 76% (24).

Multiple puncture technique with bifurcated vaccination needle used by Shelly WB and Shelly ED *et al.* in their research stated a success rate of 92 percent for periungual and genital warts, which covered both men and women (19). Further, in a study conducted in immune compromised individuals with resistant warts showed 89% cure rate (21). In all these studies, the clearance rate of warts with IL bleomycin was unrelated with the duration of warts.

Other methods of bleomycin injections through microneedle patch, bleomycin impregnated tape and dermojet showed 61.9%, 69% and 89.9% cure respectively (22, 23). In our study, we selected intralesional injections at a concentration of 1mg/ml. Mild-to-moderate pain was the main problem expected in our patients during procedure, for which addition of bupivacaine hydrochloride (0.5%) to bleomycin solution helps to relieve pain better as it had a longer duration of action than lignocaine. Furthermore, analgesics were helpful to relieve persistent pain post treatment for a few days.

7. Conclusion

Common warts or verruca vulgaris is a common cutaneous manifestation of human papilloma virus that we face in the day-to-day practice as dermatologists. The patients seek care mainly concerned due to their unsightly appearance. Intralesional Bleomycin, a newer and more promising therapy is an effective and safe treatment option in the management of common warts including palmoplantar and periungual warts. It has advantages of lower dose, superior safety profile and high patient satisfaction. With the available literature, Intralesional Bleomycin could be considered as a more reliable mode of treatment in terms of therapeutic outcome in the remission of common warts.

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