Original Article

Intralesional MMR versus Intralesional Bleomycin in the Treatment of Digital Warts: A Randomized Comparative Study and Review of the Literature

Arunima Ray, Ishan Agrawal[1], Bikash R. Kar[1]

Department of Dermatology, Christian Medical College, Vellore, Tamil Nadu, India, [1]Department of Dermatology, IMS and SUM Hospital, Bhubaneswar, Odisha, India

Abstract

Introduction: Warts are benign hyperkeratotic viral infections poorly responsive to most treatment modalities. Commonly used destructive methods can cause the scarring of the digits. Intralesional agents are preferred in digital warts. Individual efficacy has been assessed, but previously intralesional bleomycin and immunomodulator measles, mumps, and rubella (MMR) vaccine have not been compared. **Objectives:** To assess the effectiveness and safety of intralesional bleomycin versus intralesional MMR vaccine in the treatment of digital warts. **Materials and Methods:** All consenting adults with ≤5 digital warts were randomly divided into two groups by chit method: group A got intralesional MMR vaccine and group B got intralesional bleomycin monthly for 3 months with follow-up at the fourth month. Clearance and reduction in wart sizes and side effects were noted. **Results:** Totally 45 patients completed the study, and with single injection, clearance in group B was significantly higher than in group A ($P = 0.001$, Chi-square test). Necrosis, eschar formation, and residual pain were seen in group B. Overall, there was no significant difference in clearance rates at three injections ($P = 0.198$, chi-square test). **Conclusion:** Intralesional MMR vaccine and intralesional bleomycin are both effective in treating digital verrucae. Faster clearance is seen with intralesional bleomycin, with more side effects such as necrosis, eschar, and pain, controlled with oral analgesics.

Keywords: Bleomycin, digital warts, intralesional, MMR, verruca

Introduction

Cutaneous human papilloma virus (HPV) infection manifests as common warts, or verruca. Verrucae appear as firm keratotic papules over the skin and any mucosal surface. They are a cause for considerable psychological and physical morbidity.[1]

Nongenital warts occur in almost 10% of the general population, commonly in young adults. Spontaneous regression is seen in about 65%–78% of immunocompetent individuals, but it can take up to 2 years for clearance.[2]

Warts are characteristically stubborn and persist even with treatment, which is stressful for the patients as warts tend to spread over the affected region. There is no established treatment that shows 100% cure rate in clearing of warts.[2]

HPV is directly inoculated through minute channels with trauma and microabrasions. The virus targets basal keratinocytes, where the latent viral body survives leading to recurrence and poor clearance.[3]

Common treatment procedures include destructive modalities such as cryotherapy and ablative cautery. Such procedures when done on the digits take longer to heal, while interfering with the patient's daily life. Large, residual nonhealing wounds, as a sequela to these procedures, are a major deterrent for such treatment.[4,5]

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Address for correspondence: Dr. Ishan Agrawal, Department of Dermatology, IMS and SUM Hospital, Bhubaneswar, Odisha 751003, India.
E-mail: ishanagrawal1995@gmail.com

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Bleomycin is a cytotoxic glycopeptide, which binds with cellular DNA, and causes the scission of DNA strand with elimination of purine and pyrimidine bases.[6]

Immunotherapy with various intralesional agents has shown good results. These injected agents trigger a delayed hypersensitivity reaction to the virus that affects both viral antigen and infected keratinocytes.[7] Among these, measles, mumps, and rubella (MMR) vaccine is commonly available and shows good results.[8,9]

Although previous studies have assessed the individual efficacy of these agents, no available study has compared them in the treatment of digital warts.

Our study compares the effectiveness of intralesional bleomycin with intralesional MMR vaccine in the treatment of digital warts with an assessment of their side effects.

Materials And Methods

This is a prospective, randomized, single-blinded, comparative study that was conducted at a tertiary care center in Eastern India over 6-month duration. The approval of Institutional Ethics Committee was taken before starting the study. An estimated sample size calculated using online software (Raosoft software, EZSurvey 2007, Seattle, WA) was 48.

Our study included adult patients (between 18 and 65 years of age), with digital warts ≤5 in number and each wart would be between 0.25 cm and 3 cm in size. We excluded patients who were pregnant or breastfeeding, with known hypersensitivity to either agent, with flu-like sympoms, with any known peripheral vascular disease, renal disease, pulmonary disease, or cardiac comorbidities.

The patients were randomized into two groups (group A and group B) based on the chit they selected. Group A received intralesional MMR vaccine and group B received intralesional bleomycin. Injections were given once every month for a total of 3 months. The follow-up of enlisted patients was done in the fourth month. Results were evaluated by an independent, blinded dermatologist before each sitting. Changes were noted as complete clearance, partial decrease in wart size, or no change in the wart size. Complete clearance was the clearance of wart and restoration of normal skin markings at the affected site.

For MMR vaccine (TRESIVAC; Serum Institute of India Pvt. Ltd., Pune, India), 0.5 mL of vaccine was reconstituted with distilled water, and size proportionate dose was given in multiple warts.

For the preparation of bleomycin, lyophilized powder (15 mg) was dissolved in 5 mL of distilled water, with a final concentration of 3 mg/mL. This was our stock solution, which can be kept at 4°C–8°C, and used within a month. Then, 1 mL of bleomycin solution was mixed with 2 mL of 2% lignocaine inside a 5-mL syringe with a final concentration of 1 mg/mL of bleomycin. A maximum of 2 mL of bleomycin was given in each session.[10]

The agents were injected into the warts till blanching was seen. For both groups, immediate side effects, during the time of injection, and delayed side effects after injection were noted. For postinjection pain, patients were prescribed oral diclofenac as and when necessary.

Photographs were kept at baseline and after 3 months.

Statistical analysis

The reduction of size was compared after the first injection and after the third injection between both groups using a chi-square test to calculate value of probability (*P* value). At 95% confidence interval, with four degrees of freedom, values less than 0.05 were considered significant.

Results

Totally 48 patients with digital warts were included. All patients were between 18 and 30 years of age. Group A had 16 males and seven females, whereas group B had 13 males and nine females; three patients (one from group A and two from group B) dropped out after the first injection for unknown reasons [Figure 1].

Of 23 patients in group A, 20 patients responded to intralesional MMR vaccine, 5/23 patients (21.7%) showed complete clearance after the first injection, and 4/23 patients (17.3%) showed complete clearance after the second and third injections each. In 7/23 patients (30.4%), there was only a partial reduction in size on final follow-up [Figure 2].

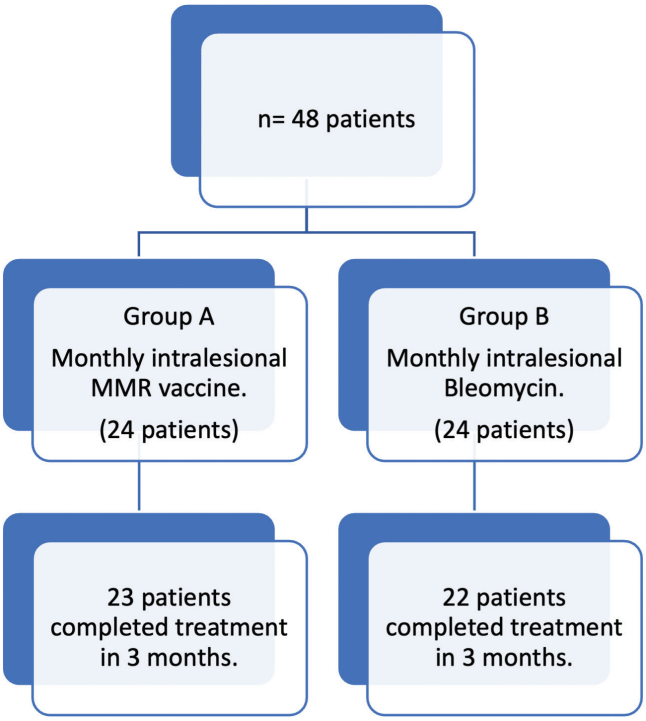

Figure 1: Patients' flow chart

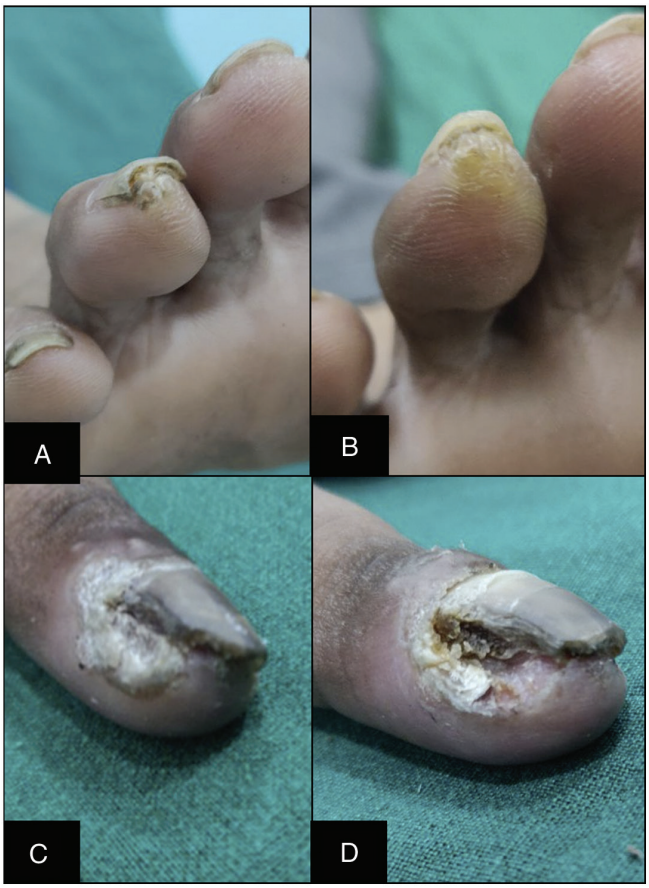

Figure 2: (a) and (b) Patient 1, and (c) and (d) patient 2 showing the partial clearance of digital wart with three sittings of MMR vaccine

Of the 22 patients in group B, all the subjects showed improvement compared with baseline after three injections. Seventeen of 22 (77.2%) patients showed complete clearance after the first injection and 2/22 (9%) showed complete clearance after two injections. The remaining 3/22 patients (13.6%) had partial reduction in size on final follow-up [Figure 3] [Table 1].

At the end of the study, complete clearance was seen in 56.5% of patients of group A and 89% of patients of group B. Both groups experienced pain during injection, and pain was relatively more in patients of group B. Postinjection pain (>12 hours) was present in four (17.4%) patients of group A and 20 (86.9%) patients of group B. Patients in group A found the pain tolerable and did not need more than two to three doses of analgesic. Patients in group B had considerable pain and needed three to six doses of analgesic. Two patients in group B had pain that lasted till 72 hours.

Necrosis and eschar formation was seen in wart site in 21 patients of group B [Figure 4]. Other side effects like pigmentary changes, residual scarring, nail dystrophy, Raynaud's phenomenon, and postinjection flu-like symptoms were not seen in any of the patients [Table 2].

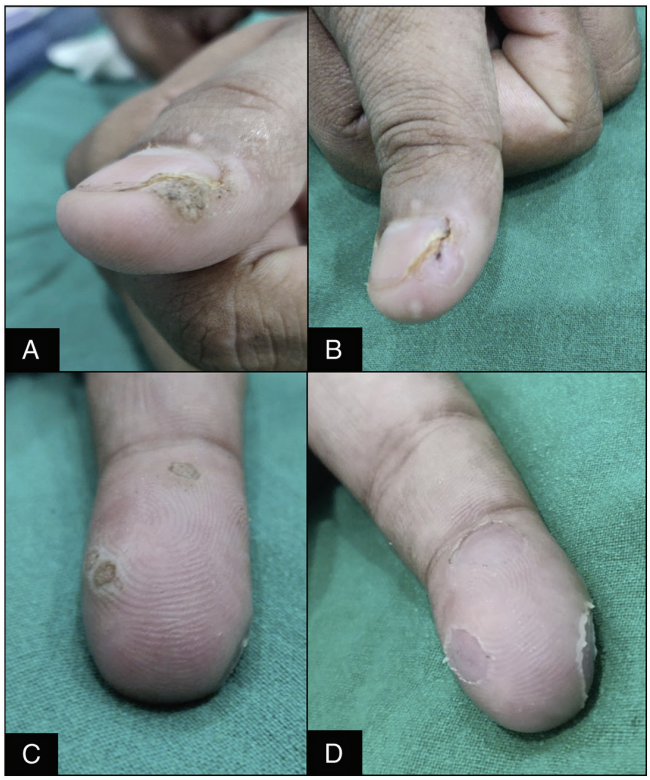

Figure 3: (a) and (b) Patient 1, and (c) and (d) patient 2 showing the complete clearance of digital wart with a single sitting of bleomycin

Discussion

Common warts are hyperkeratotic, exophytic papules, or plaques occurring anywhere in the body. The causative organism HPV targets the basal keratinocytes and replicates in the upper stratum spinosum and granulosum. The lack of spontaneous resolution in otherwise healthy individuals could be due to subdued local immunity.[11]

Nongenital warts occur in almost 10% of the general population, commonly in young adults. Spontaneous regression is seen in warts, in almost 65%–78% cases, and it can take almost 2 years for clearance.[2]

Common warts are frequently HPV types 1, 2, 4, 27, 57. Concurrent infection may be seen due to more than one HPV type. Pseudo-inoculation is generally seen where minor cuts and abrasions become a channel for the virus to enter and lodge in the basal keratinocytes.[2]

Because the hands are vulnerable to undetectable microtrauma, patients frequently present with multiple digital warts. Commonly, warts are treated with destructive modalities including cryotherapy and surgical removal by curettage or cautery.[2]

Cryotherapy can cause considerable pain, erythema, bullae, and ulceration.[12] Surgical removal causes problematic scarring over the fingers and may damage the nail apparatus when used to clear periungual warts.[2] Additionally, cutaneous warts are omnipresent,

Table 1: Results of groups A and B

	MMR vaccine, group A	Bleomycin, group B	*P* value
Complete clearance after the first injection	5/23	17/22	0.001757, chi-square test
Complete clearance after the second injection	4/23	2/22	
Complete clearance after the third injection	4/23	0/22	
Partial reduction in size after three injections	7/23	3/22	
Complete clearance in three injections	13/23	19/22	0.198679, chi-square test

Table 2: Adverse effects in groups A and B

Side effects	Bleomycin	MMR vaccine
Pain during injection	+++ (22/22)	++ (23/23)
Pain after injection	+++ (20/22)	+ (4/23)
Necrosis and eschar formation	++ (21/22)	− (0/23)
Pigmentary changes	–	–
Scarring	–	–
Raynaud's phenomenon	–	–
Nail dystrophy	–	–

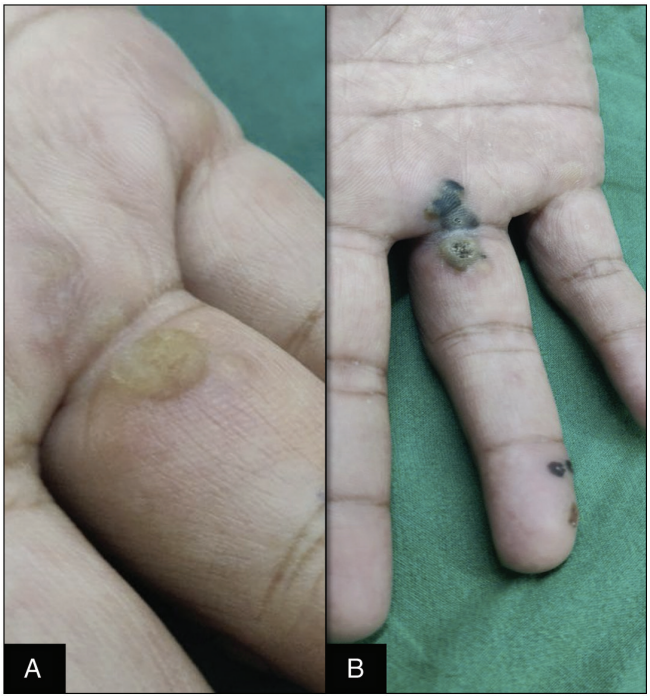

Figure 4: (a) Before and (b) after photographs showing necrosis after 2 days of intralesional bleomycin

but access to surgical equipment and cryotherapy may be limited in many setups, which makes intralesional therapy a more convenient treatment option for dermatologists.

Over the fingers and toes, this is difficult because patients cannot completely rest these sites, and even with minimal work, they are likely to get exposed to different physical and chemical agents with continued microtrauma. This makes injectable therapy a preferable option for the treatment of digital warts.[13] Our study compares intralesional bleomycin with intralesional MMR vaccine because these two injectable agents have not been previously compared.

Bleomycin is an antibiotic, sourced from *Streptomyces verticillus*. It is excreted by renal pathways, and tissue metabolism is due to bleomycin hydrolase enzymes in different tissues. The enzyme is least active in the lungs and skin, which explains the toxic manifestations of the drug at these sites.[14]

Bleomycin acts by cutting DNA strands, and in the cutaneous tissue, there is keratinocyte apoptosis, endothelial cell sclerosis, and inhibition of collagen synthesis.[14] Bleomycin in warts works by inducing necrosis. In intralesional injection, the drug must be deposited mid-dermis.[14]

Multiple modalities of drug administration include microneedling devices, mechanical jet injectors, and electrochemotherapy.[15]

Local cutaneous adverse reactions are pain, erythema, edema, and eschar formation. There may be residual scarring and pigmentary changes in the long term. Bleomycin is commonly found, and the intralesional technique is easy to use, with minimal equipment, which makes it an easy-to-use modality in daily clinical practice. Studies have shown that adding local anesthetic to bleomycin shows better clearance rates in common warts. Local anesthetics have shown changes in cell permeability, which increases bleomycin uptake by cells.[15]

Different studies with bleomycin are listed in Table 3.

The clear advantages of using intralesional MMR are its wide availability, its extensively studied side effects, and its established safety even in children.[9] MMR vaccine works via immunotherapy, by eliciting a nonspecific HPV antigen response and mounts a local immune reaction.

Immunotherapy jump starts a localized delayed hypersensitivity reaction, which also helps clear the distant warts.[30] There is a release of interleukin (IL)-2, IL-12, interferon (IFN)-gamma, and tumor necrosis factor (TNF)-alpha. The immune response once triggered persists for some time, which avoids recurrence.[31]

Several studies with MMR vaccine in the treatment of warts are enlisted in Table 4.

Patient compliance and follow-up is a cause for concern in asymptomatic dermatological diseases including warts.

Table 3: Studies with intralesional bleomycin in different warts and their common side effects

Number	Author	Complete clearance rate	Method of injection	Wart type	Side effects
1	Al-Naggar *et al.*[16] (2019)	70% 83.3%	Intralesional and microneedling	Plantar warts	Pain, erythema, and transient induration
2	Barkat *et al.*[17] (2018)	69.3%	Intralesional	Plantar warts	Pain
3	Singh Mehta *et al.*[10] (2019)	80%	Intralesional	Common warts	Pain, scarring, and hyperpigmentation
4	Di Chiacchio *et al.*[18] (2019)	50% 85.7%	Intralesional and intralesional + electroporation	Ungual warts	Hemorrhagic necrosis, moderate pain, onycholysis, reflex sympathetic dystrophy, infection, ulceration
5	Soni *et al.*[15] (2011)	96.47%	Intralesional	Palmoplantar and periungual warts	Pain, eschar
6	Unni and Tapare[6] (2017)	93.10%	Intralesional	Common warts	Eschar, hypopigmentation, hyperpigmentation, scarring
7	Hodeib *et al.*[19] (2021)	85%	Intralesional	Plane warts	Pain, hypopigmentation, hyperpigmentation, itching, and scarring
8	Gamil *et al.*[20] (2020)	83.3%	Topical bleomycin with microneedling	Plantar warts	Pain, erythema, edema, and hyperpigmentation
9	Suh *et al.*[21] (2020)	82.35%	Topical bleomycin after fractional ablative lasers	Periungual warts	Pain, hyperpigmentation, pinpoint bleeding
10	AlGhamdi and Khurram[22] (2012)	74%	Low concentration intralesional bleomycin (0.1 U/mL)	Plantar warts	Moderate pain
11	Kruter *et al.*[23] (2015)	74%	Intralesional	Common warts	Pain, erythema, pigmentation, blistering, callosity, and transient nail dystrophy
12	Dobson and Harland[24] (2014)	92%	PDL followed by bleomycin	Recalcitrant common warts	Pain, blistering, crusting
13	Pasquali *et al.*[25] (2017)	78%	Intralesional bleomycin with electroporation	Periungual warts	Pain, erythema, and dyspigmentation
14	Alghamdi *et al.*[26] (2011)	86.6%	Diluted bleomycin with translesional multipuncture technique	Periungual warts	Pain and hyperpigmentation
15	Konicke and Olasz[27] (2016)	3/3 clearance	Bleomycin + microneedling	Recalcitrant plantar warts	Pain and necrosis
16	Lee *et al.*[28] (2015)	73.3%	Intralesional bleomycin	Genital warts	Pain, dyspigmentation, scarring
17	Castro-Ayarza *et al.*[29] (2020)	8/8 cases with average of three sessions	Intralesional bleomycin	Periungual plantar digital warts	None

PDL = pulsed dye laser

Table 4: Studies with intralesional MMR vaccine in different warts and their common side effects

S. no	Author	Complete clearance rate	MMR vaccine	Wart type	Side effects
1	Rezai *et al.*[7] (2019)	72.5%	Intralesional	Common warts	Lesional pain
2	Shaldoum *et al.*[32] (2020)	80%	Intralesional	Common warts	Lesional pain and erythema
3	Zamanian *et al.*[9] (2014)	75%	Intralesional	Common warts	Pain and flu-like symptoms
4	Jaiswal *et al.*[30] (2020)	60%	Intralesional	Common warts	Lesional pain, erythema, and PIH
5	Gupta *et al.*[33] (2020)	30.3% 21.2%	Intralesional and intradermal	Common warts	Pain and erythema
6	Awal and Kaur[13] (2018)	68%	Intralesional	Common warts	Lesional pain, erythema, and flu-like symptoms
7	Nofal and Nofal[34] (2010)	81.4%	Intralesional	Common warts	Pain and flu-like symptoms
8	Saini *et al.*[35] (2016)	46.5%	Intralesional	Common warts	Pain
9	Abd El-Magiud *et al.*[12] (2020)	70%	Intralesional	Common warts	Pain and flu-like symptoms
10	Chauhan *et al.*[36] (2019)	82.4%	Intralesional	Common warts	Pain at the injection site
11	Choi *et al.*[37] (2011)	26.5%	Intralesional	Common warts	Pain
12	Nofal and Alakad[38] (2020)	73%	Intralesional	Anogenital warts	Pain and flu-like symptoms
13	Nofal *et al.*[8] (2015)	63%	Intralesional	Recalcitrant warts	Pain, itching, and erythema

PIH = post-inflammatory hyperpigmentation

A faster clearance rate achieved in one sitting is much more desirable. We thereby assessed the number of sittings taken to show complete clearance in the warts. Our study shows such a desirable result of early complete clearance, with a single dose with bleomycin.

In our study, 77.2% of cases treated with intralesional bleomycin had clearance in one sitting, whereas intralesional MMR had 21.7% clearance with single sitting.

The bone of contention with bleomycin is the pain and eschar formation. Both these adverse effects can be formidable for patients especially occurring over the fingers. With adequate oral analgesics and preprocedural counseling, these side effects were tolerated in our patients.

Immunotherapy in cutaneous warts includes IFN-alpha, topical imiquimod 5%, contact allergen, systemic immunotherapy (zinc) and HPV vaccine, intralesional antigen injection of Candida, *Trichophyton rubrum*, purified protein derivative, Bacille Calmette-Guerin (BCG), or MMR.[39]

Among these, BCG is considered inferior, whereas the rest have comparable efficacy among themselves.[40]

A search of the available literature showed a complete clearance of common warts with MMR vaccine ranged between 70% and 80%. These studies often did not observe complete clearance with just one sitting, and latency was seen between injection and clearance of warts.

Different studies and their results with MMR vaccine are enlisted in Table 2.

Common side effects included pain during injection and flu-like illness. In our study, all the patients had pain during injection, but flu-like illness was not seen.

Comparatively, pain during injection was more with bleomycin and persisted in all patients receiving bleomycin with a need for multiple doses of oral analgesic. Other than pain and eschar formation, more grave side effects such as scarring, dyspigmentation, and Raynaud's phenomenon were not seen in any of our patients.

Conclusion

Both intralesional bleomycin and MMR are effective in the treatment of digital warts. But significantly higher clearance rate with a single injection is seen with intralesional bleomycin. Side effects such as prolonged pain and eschar formation are also seen in bleomycin. A major limitation of our study is a short follow-up period. Because verrucae are notoriously recurrent, delayed clearance with MMR vaccine has been observed.

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None.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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