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Original Research Article

Intralesional immunotherapy with Bacille Calmette- Guerin (BCG) vaccine for the treatment of cutaneous warts

Amisha Kukreja[1], Karaninder Singh Mehta[1,*], Pushpinder Singh Chauhan[1], Sanket Vashist[1], Sheenam Hooda[1], Anju Lath Sharma[1], Anuj Sharma[1], Reena Sharma[1], Prabal Kumar[1], Ravinder Singh[1], Sujaya Manvi[1], Priyanka Thakur[1], Rohit Negi[1]

[1]*Dept. of Dermatology, Venereology & Leprosy, Dr. Rajendra Prasad Govt. Medical College Tanda, Kangra, Himachal Pradesh, India*

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ABSTRACT

Background and Aims: Myriad of therapeutic modalities for warts are available but none promises complete response. Despite adequate treatment, the virus may persist in the surrounding tissues leading to recurrence. Immunotherapy is considered better than destructive options where there are multiple lesions, extensive involvement and is best suitable for paediatric patients. The aim of the study was to evaluate the efficacy and safety of intralesional BCG vaccine in the management of cutaneous warts (common warts, plantar and periungual warts).

Materials and Methods: Patients of age 12 years and above clinically diagnosed with cutaneous warts and presenting consecutively in the outdoor clinic of Dermatology, Venereology & Leprosy Department of Dr. R.P. Govt. Medical College, Kangra at Tanda, Himachal Pradesh between June 2021 to May 2022 were enrolled. BCG vaccine was administered into the largest wart intralesionally and the injection was repeated every 3 weeks for a maximum of four injections or till the complete clearance of warts, whichever was earlier. The efficacy was assessed every 3 weeks and patients were followed up at 3 and 6 months.

Observations: Majority of patients were in the age group of 14-53 years. The study showed therapeutic response in 35.08% (20/57) patients and partial response in 63.15% (36/57) patients while there was no response in 1.75% (1/57) patients at the end of 12 weeks with a very low recurrence rate (5.2%). Plantar warts have responded excellently showing complete clearance in 91.5% and partial response in 9.5% of the patients followed by palmar warts achieving complete response in 60% and partial response in 40% of the patients.

Conclusion: The reconstituted BCG immunotherapy is a cheap, effective and easily available therapeutic option which can easily be practised routinely. However, due its considerable adverse effects as compared to other immunotherapeutic agents, we do not recommend it to be the first line agent.

1. Introduction

Verrucae (warts) are very common benign proliferation of the skin, caused by the HPV, the most common presentations being common warts or verruca vulgaris (70%), plantar warts and flat warts.[1] HPV is an epitheliotropic DNA virus. Any breach in epithelia serve as a channel through which HPV infects the keratinocytes.[2,3] Mode of spread of HPV is either by direct contact or via environment. Most frequently, verrucae manifest as polymorphic warty papules or plaques and over 100

* *Corresponding author.*
E-mail address: drkaranindermehta@gmail.com (K. S. Mehta).

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different types of HPV infecting different sites of the body have been reported. Common warts are mainly caused by HPV 2 but can also be caused by type 1, 4, 27 and 57. Most common cause of plane warts are HPV type 3 and 10 while plantar warts are usually caused by HPV 1, 2, 4, 27 or 57.[4] Genital-mucosal warts are caused by HPV 6, 11, 16 and 18 whereas others such as Epidermodysplasia verruciformis show specifc association with HPV 5 and 8. In spite of spontaneous resolution in a number of cases, therapy is required in many patients for which various modalities have been tried (destructive procedures, excision, hypothermia, topical and intralesional immunotherapy, hyperthermia, psychological methods, etc.) with variable outcomes and patient satisfaction rates.[5] Intralesional immunotherapy enables the immune system to mount a delayed type of hypersensitivity reaction not only against certain bacterial and fungal antigens but also against Human Papilloma virus. Different antigens such as measles mumps rubella (MMR), mumps, candida trichophyton, bacille calmette-guerin (BCG), purified protein derivative (PPD), etc. are being employed in intralesional immunotherapy which has been proved superior to traditional therapy.[6] BCG vaccine, with its over a century of availability, economic viability and use experience, could be a very useful modality for wart treatment in resource poor countries of the developing world.[7]

2. Materials and Methods

Patients of age 12 years and above clinically diagnosed with cutaneous warts (common warts, plantar and periungual warts) and presenting consecutively in the outdoor clinic of Dermatology, Venereology & Leprosy Department of Dr. R.P. Govt. Medical College, Kangra at Tanda, Himachal Pradesh between June 2021 to May 2022 were enrolled for the study after informed written consent. The study was conducted after necessary approvals from Institutional Protocol review Committee and Institutional Ethics Committee.

2.1. Exclusion criteria

Following patients were excluded from the study:

1. Pregnant and lactating women.
2. Children < 12 years.
3. Patients with plane warts and genital warts.
4. Patients with immune suppression from any disease or drug therapy.
5. Active case of tuberculosis or past history of TB.

2.2. Methods

2.2.1. History and clinical examination

Clinical details regarding age, gender, duration of warts, their location, number, dimensions and clinical type was recorded. Pre procedure counseling included details of procedure, potential benefits and possible immediate injection site pain and swelling during first 24 to 72 hours.

2.2.2. Treatment protocol

Freeze-dried BCG was reconstituted with 1 ml of normal saline (diluent) using sterile syringe and sterile needle. All the eligible patients were given 0.1 ml BCG intralesionally into the single largest wart, in a 30G insulin syringe holding parallel to skin surface with bevel end facing in upward direction (Figure 1).[8] The injection was repeated at an interval of 3 weeks on the same wart or another wart depending upon the regression of previously injected wart. The injections were given for total of four treatment sessions (0, 3, 6, 9 weeks) or till complete clearance whichever was earlier. First follow up was done after three months and second follow up after six months of the first injection, to detect any recurrence after clearance of warts. Patients were prescribed tablet diclofenac (50 mg twice daily) for post injection erythema, swelling and pain during first 2-3 days.

2.2.3. Evaluation for therapeutic outcome

Clinical photographs were taken at baseline, and follow up visits for pretreatment and post treatment comparision. Subsequently, patients were advised to report anytime in case of recurrence. Immediate and late adverse effects of BCG were evaluated after each treatment session.

The clinical response were graded as shown in Table 1.

Table 1: Grades of improvement

Grades	Definition
Complete clearance	Complete clearance of all warts, evidenced clinically by total disappearance of the hyperkeratosis and thickening of skin
Partial clearance	Residual warts still visible
No response	No change in size and texture
Recurrence	Recurrence during the study period

Patient satisfaction score was assessed based on Likert scale (Table 2).

Table 2: Likert scale for patient satisfaction score

Satisfaction level	Score
Very much satisfied	5
Somewhat satisfied	4
Undecided	3
Not really satisfied	2
Not at all satisfied	1

Statistical analysis MS Word Excel software was used to tabulate and analyze the data. The continuous data are presented as means±standard deviation (SD) and categorical variables are presented as frequencies and percentages.

3. Results

Twenty seven patients did not complete the study due to various reasons. Fifteen patients were lost to follow up after the first dose and twelve patients did not turn up after second dose.

Table 3: Depicts baseline characteristics of the patients.

Baselinecharacteristics		Number of patients (%) n =57
Gender	Males	39(68.4)
	Females	18(31.6)
	M:F	2.1:1
Age inyears	Range	14-53
	Mean±SD	27±8.81
	14-20	18(10.26)
	21-40	36(20.52)
	41-53	3(1.71)
Duration of warts	Range	1month-16 months
	Mean±SD(months)	4.85±3.51
	<6months	38(66.66)
	6months-1year	17(29.82)
	>1years	2(3.50)
Number of warts	Range	1 -50
	Mean	10.36±2.95
	<5	26(45.61)
	5-10	9(5.13)
	>10	22(12.54)

Table 3 depicts baseline characteristics of the patients. The 57 patients who completed the study comprised 39 men and 18 women (male: female 2.1:1). Their ages ranged from 14 to 53 with mean±SD 27±8.81 months, while the duration ranged from 1 to 16 months with mean±SD of 16±8.45 months. Thirty eight (66.66%) patients had them for less than 6 months while 17(29.8%) patients had them for duration between 6 months to 1 year. Majority (96.4%) of the patients had warts for less than one year. The number of lesions in each patient ranged from 1-50 with mean±SD of 10.43±11.01 and majority [31 (54.3%)] patients had <10warts.

Table 4 depicts distribution and size of warts. Overall, there were 591 warts in 57 patients and included 178(30.1%) plantar warts, 28(4.2%) palmar warts and 21(3.5%) periungual warts. Three hundred sixty four (61.6%) warts were present over dorsal hands and feet. Two patients with plantar warts had mosaic morphology. The majority, 605(86.05%) warts measured less than 10 mm in size while 91(12.94 %) warts were between 10 and 20 mm in size.

Tables 4 and 5 show clearance of warts at every visit. Overall 20 (35.08%) patients were cleared of 326 (55.16%) warts at the end of 12 weeks study period.

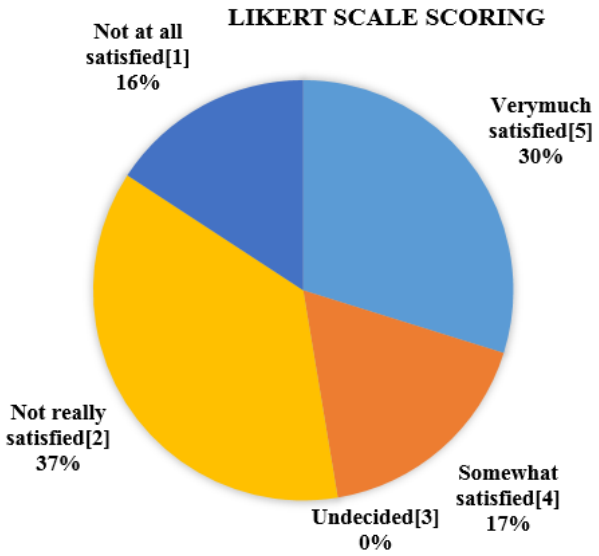

Chart 1: Likert scale scoring in study subjects

4. Discussion

Cutaneous infections caused by HPV are usually recurrent and are among the most common conditions presenting to dermatologists. Warts typically occur over dorsal hands, feet, palms and soles, and without treatment may continue to increase in size and distribution. Nevertheless, plantar and periungual warts can be painful and warts on cosmetically important areas such as face and hands may affect patient's quality of life. Although spontaneous remission occur in majority of the individuals, it tends to have more slower course and may take months to years to resolve. These individuals are most likely to become the source of infection to others.[9] Recalcitrant warts may reflect a localized or systemic cell-mediated immune deficiency to HPV. Various reasons have been hypothesized such as lack of production of memory T cells to target HPV infection, failure of clonal expansion of lymphocytes to adequate stimulation, inability of T lymphocytes to traffic to sites of infection and weak effector response. The fact that HPV causes extensive lesions in patients with Hodgkin's disease, AIDS and those on immunosuppressants furthur weighs the role of cell mediated immunity in their causation and persistence.[10] Myriad of therapies including immunotherapy, medical, surgical or other destructive procedures are available, but no single therapeutic option is completely successful in achieving complete cure and preventing recurrences.

BCG vaccine is an attenuated form of Mycobacterium bovis which is protective against TB. It is usually well-tolerated, with the vaccine site healing in about 3 months with a small scar.[17] Various immunotherapies like DCP, SADBE, imiquimod, interferon alpha and gamma, skin test antigens like Candida, mumps, trichophyton and tuberculin, vaccines like BCG vaccine, MMR vaccine, Mycobacterium

Table 4: Clearance of warts at each visits and cure rate at end of 12 weeks study period

Sites and size of warts	No. of wartsn =591	After first dose	After second dose	After Third dose	After fourth dose	Complete-clearance	Partial Response	No respons e
Sites*								
Plantar	178	134	74	42	15	163 (91.57%)	15	0
Dorsal handsandfeet	364	331	297	257	231	133 (36.53%)	224	9
Palmar	28	27	25	19	11	17 (60.71%)	11	0
Peri-ungual Skin	21	20	17	10	08	13 (61.90%)	08	0
Total	**591**	**512** (86.63%)	**413** (69.81%)	**328** (55.49%)	**265** (44.83%)	**326** (55.16%)	**258** (43.65%)	**9** (1.42%)
Size								
<10 Mm	493	425 (86.20%)	338 (68.55%)	265 (53.75%)	216 (43.81%)	277 (56.1%)	216 (43.81%)	0
10-20 Mm	91	80 (87.9%)	69 (75.82%)	58 (63.73%)	44 (48.35%)	47 (51.6%)	37 (40.65%)	7 (7.7%)
>20 Mm	7	7 (100%)	6 (85.71%)	5 (71.42%)	5 (71.42%)	2 (28.57%)	3 (42.85%)	2 (28.57%)

Table 5: Cure Rates in study subjects at each visit

Number of doses and follow upvisits	Responsetotreatment	Number of patients (%) (n=57)
Firstdose	Completeclearance	01
	Partialclearance	55
	No response	01
Seconddose	Completeclearance	11
	Partialclearance	45
	No response	01
Thirddose	Completeclearance	15
	Partialclearance	41
	No response	01
Fourth dose	Completeclearance	20
	Partialclearance	36
	No response	01

Table 6: Various studies using different immunotherapeutic agents for the management of warts.

Study	Immuno-therapeutic agent	Maxi-mum no. of sessions	Interval between two sessions (weeks)	Complete response rate (%)	Adverse Effects
Buckleyet al [11]	DCP	3	1-4	88	Painful vesiculation, Eczematous eruption, Flu like symptoms and Inguinal lymphadenopathy
O Kose et al [12]	IFN-alpha-2a	3	3	40	Injection site reactions, Fever, Malaise, Nausea and Vomiting
Johnson et al [13]	Mumps or Candida	3	3	74	Immediate pain, Pruritus
Sharquieet al [14]	BCG vaccine	3	4	40	Nil
Singh et al [15]	Mw vaccine	10		55	Intradermal granuloma, Pain Paresthesia, Atrophic scarring
Nofal and Nofal [6]	MMR vaccine	5	2	85	Flu-like symptoms, Erythema, Edema, Pain, and Itching
Saoji et al [16]		4	2	76	Erythema, Edema, Pain

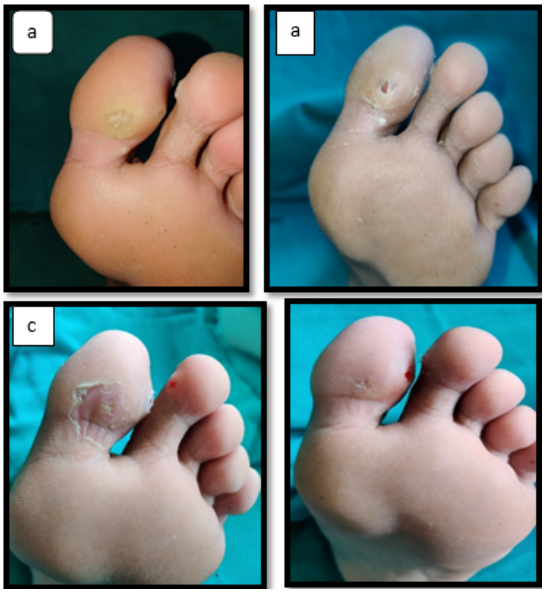

Fig. 1: a: Warts over the plantar surface of left feet; **b:** Three weeks after first dose of BCG over the largest lesion; **c:** Complete clearance of the target wart and next injection is given on another wart. Partial clearance of other warts; **d**: Complete clearance of all the warts after the third dose leaving behind scarring.

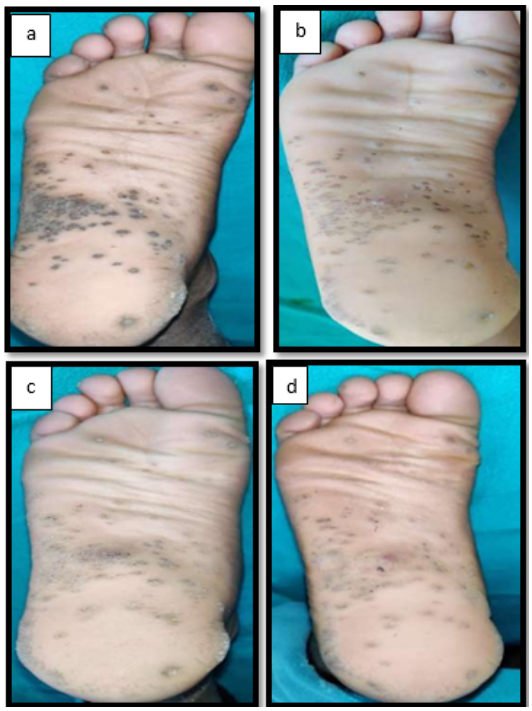

Fig. 2: a: Multiple warts over plantar surface of right foot(baseline); **b:** Targeted and non targeted warts showing significant clearance at 3 weeks after 1st dose of intralesional BCG; **c**: Warts still visible with erythema and abscess formation at the injection site; **d**: Partial clearance of warts after the 4th session of BCG therapy

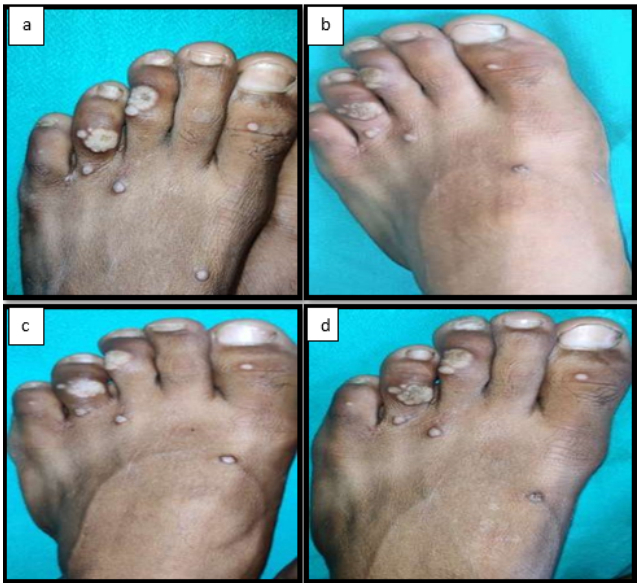

Fig. 3: Multiple warts over dorsal left foot. **a:** Three weeks after first dose; **b:** After second dose; **c:** After third dose; **d:** After fourth dose of intralesional BCG into the largest wart. No change in size and textutre of any of the warts; patient did not respond to intralesional BCG.

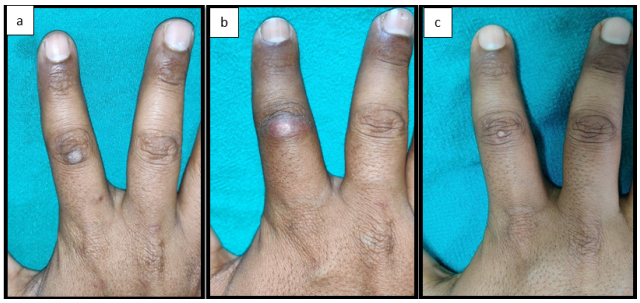

Fig. 4: a: Wart over dorsum of index finger of right hand; **b:** Complete clearance at 3 weeks after one treatment session. Local erythema, abscess and ulceration occur at the injection site; **c:** Recurrence of the lesion after 3 months of complete clearance at the same site. The abscess resolved without leaving any sequale.

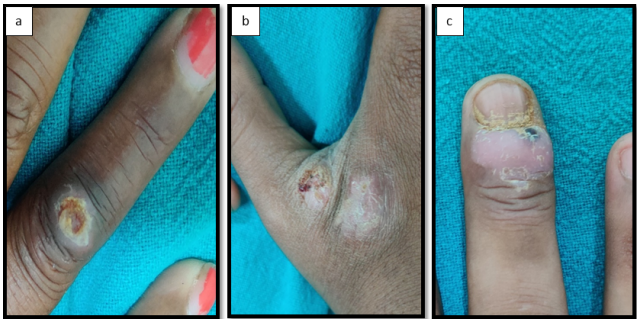

Fig. 5: Local Adverse effects: Abscess and ulceration following intralesional BCG over; **a:** Dorsal surface of base of right thumb; **b:** Dorsal aspect of left index finger and **c:** Periungual area of middle finger of right hand but preserving the nail unit.

w (Mw) vaccine and autologous vaccine have been tried by different study groups with varying results.

In the present study, age range of patients was between 14-53 years, which is slightly higher than that of study done by Jaisanghai et al[7] (18-46 years) and Sharique et al[14] (6-41years). The male to female ratio in our study was 2.1:1. However, it was higher as compared to previous studies done by Rajashekar et al[8] (1.6:1) and Podder et al[18] (1.53:1). While Jaisanghai et al[7] selected only male population, female preponderance was reported by Kenawi et al[19] (0.76:1). In the present study, the mean number of warts was 10.36±2.95 with a range between 1-50, which is comparable to other similar studies. Our study showed therapeutic response in 35.08% (20/57) patients and partial response in 63.15% (36/57) patients while there was no response in 1.75% (1/57) patients at the end of 12 weeks. Comparably, Sharique et al[14] in their placebo controlled double blind study injected 1-3 doses of 0.1 ml BCG intradermally in the upper arm at an interval of 4 weeks, achieved complete response in 39.7% of the patients and reported intralesional BCG to be superior in efficacy as compared to the placebo arm. Similarily, in a study conducted by Rajashekhar et al[8], 13 patients were injected 0.1 ml BCG intralesionally into the largest wart at an interval of 2 weeks for maximum of four sessions and reported complete response in 30.8% of the patients and partial response in 38.4% of the patients. However, they concluded PPD therapy (CR=35.3%) to be marginally superior than BCG therapy (CR=30.8%) in terms of efficacy and side effect profile. On the other hand, a higher number of patients achieved complete response (70%) in a study of 30 patients done by Rao et al[20] in which they injected the largest wart with 0.1 ml of BCG, repeated every 3 weeks for a maximum of 5 sessions.

The recurrence rate in our study is handsomely low (5.2%) with only one patient out of 20 with complete response reported recurrence at the same site after 3 months of achieving the complete clearance.

In the present study, plantar warts have responded excellently showing complete clearance in 91.5% and partial response in 9.5% of the patients followed by palmar warts achieving complete response in 60% and partial response in 40% of the patients. Jagati et al[21] in their study reported similar results with 86.66% and 13.3% patients of palmoplanter warts showing complete resolution and partial response respectively at the end of 6 weeks. In the same study, they observed 100% therapeutic response in periungual warts and 60% complete response in patients of common warts. Conversely, our study reported lesser therapeutic response in periungual warts (61.9%) followed by warts on dorsum of hands and feet(36.5%). Only one patient with multiple warts on dorsum of feet did not respond at all after 4 injections of intralesional BCG in the target wart at the end of 12 weeks study period.

In the present study, 46 out of 57 patients had distant warts. However, 28.07% patients showed complete clearance and partial reasponse was seen in 70.17% of the patients. Whereas, 1.8 % did not respond at distant non-injected warts at the end of 12 weeks. This is in contrast to a study by Jaisanghai et al[7] that reported 75% complete response in the distant warts. This discordance can be explained by the fact that the patients having multiple warts in their study design were less(30%) as compared to that of our study(80%). Nonetheless, in our study, majority of the patients with near and distant lesions responded either completely or partially emphasizing the role of cell mediated immunity as reported by other studies. Injection of the antigen stimulates the cascade of mononuclear cell proliferation which promotes Th1 cytokine responses, particularly interferon-gamma and interlekuin. This furthur leads to activation of cytotoxic T cells and natural killer cells that help to eradicate human papillomavirus infected cells. It is also proposed that antigen immunotherapy can stimulate tumor necrosis factor-α and interlekuin 1 release, downregulating gene transcription of human papillomavirus. The ability of the antigen to change the cytokine milieu to a Th1 response pattern triggering a cell mediated immune response against the human papillomavirus seems to be the cornerstone of immunotherapy.

In the present study, out of 20 patients showing complete response, majority (75%) of the patients responded with 3 injections. Fifty five percent (11/20) of patients showed complete resolution even after the second dose. Rest 25%(5/20) required fourth dose. Except for only one patient, all other patients responded to all the 4 doses either partially or completely. Similarily, In a study by Kenawi et al[19], 39.3% patients showed complete clearance after third session of intralesional BCG.

We observed 50.1% cure rate for lesions sized <10mm and 51.6% cure rate in lesions sized between 10 and 20 mm as compared to lesions of size >20 mm (28.57%) indicating that the size of the wart before the treatment is an important factor in predicting therapeutic response. Also patients with lesser number of warts achieved therapeutic outcomes earlier than those having larger number of lesions.

The duration of the warts is another important prognostic factor. Our study has reported better and quicker response rates in the patients having warts of recent onset. In accordance with this, Bruggink et al[22] documented lower cure rates among patients whose warts had been present for six or more months than among those whose warts had been present for a shorter duration, furthur validating our study results. On the contrary, Rao et al[20] showed that the longer the wart duration better the response to therapy.

Almost all the studies had used BCG vaccine dose range from 0.025 ml to 0.5 ml either intralesionally or intradermally with variable results.[9] Gupta SK[23], in a

case report of patient with multiple genital warts, injected intralesional BCG in a dose of 0.1 ml/cm2 (the maximum being 0.5 ml or injecting 5 warts) in one sitting. In yet another study by Fayed et al,[23] 30 patients received a local cervical injection of 0.5 mL of a solution containing 0.025 mg of BCG vaccine in the affected area. Sharique et al[14] and Podder et al[18] injected BCG intradermally and obtained significant cure rates with less side effects. However, in our study, we chose the most frequent used dose (0.1ml) and injected it intralesionally that too into the single largest wart. Our experience with intralesional BCG immunotherapy is in concordance with previous reported studies. Furthermore, our cure rates are well comparable to other skin test antigens and vaccines for the treatment of warts as the clearance rate of warts with various immunotherapies other than BCG vaccine ranged from 39.7 to 87%.[21]

Most common side effect observed was pain during injection(95%) followed by abscess, ulceration and scarring(60%), erythema(49%) and flu like symptoms(14%). These side effects caused major discomfort to the patients and was one of the leading reasons for the drop outs. Also, abscess formation at injection site after 1st or 2nd injection, caused delay in subsequent doses. Similar side effect profile was reported by Rao AG[18] and Kenawi et al[19]. In three case series of seven patients, Daulatabad et al[24] has reported BCGitis in one and lymphadenopathy in three patients, which were treated with isoniazid and rifampicin in the Indian setting and highlighted the danger of BCG in endemic areas. Another study had put forward the controversial role of anti-tuberculous agents for the management of regional BCG complications due to the emergence of resistance to Pyrazinamide, Isoniazid and more recently to Rifampicin. Similarily, for management of suppurative adenitis, various surgical options such as repeated needle aspiration and surgical excisions are advocated, however definitive management is not yet defined.[25]

Forty seven percent of the patients were satisfied (satisfaction score of 4 to 5 on likert scale) while a major proportion of fifty-three percent patients were not satisfied (satisfaction score of 1 to 2 on likert scale) with the therapeutic outcome(Table 6).

Intralesional BCG therapy appears treatment option for common warts especially for palmo-plantar warts. It addresses the limitations of ablative therapy in that it enhances the cell mediated immune response that clears the virus infected tissue irrespective of whether it is visible or not. It might also be able to target warts situated away from the site of the immunotherapeutic injection and therefore help in treating multiple warts, warts on inaccessible sites or sites where ablative therapy is difficult (e.g., subungual or periungual regions).

5. Conclusion

The reconstituted BCG immunotherapy is a cheap, effective and easily available therapeutic option which can easily be practised routinely. However, due its considerable adverse effects as compared to other immunotherapeutic agents, we do not recommend it to be the first line agent. It warrants more clinical trials to further evaluate its effectiveness and safety and to more clearly define its place in the treatment of warts.

6. Limitations

Cross-sectional study design and lack of control group are the main limitations of this study. Small sample size due to the unfortunate covid-19 pandemic and hence interruppted follow-ups are the other limitaions.

7. Conflict of Interest

None.

8. Source of Funding

None.

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Author biography

Amisha Kukreja, Junior Resident

Karaninder Singh Mehta, Professor and Head

Pushpinder Singh Chauhan, Associate Professor

Sanket Vashist, Senior Resident

Sheenam Hooda, Junior Resident

Anju Lath Sharma, Assistant Professor

Anuj Sharma, Assistant Professor

Reena Sharma, Assistant Professor

Prabal Kumar, Senior Resident

Ravinder Singh, Senior Resident

Sujaya Manvi, Senior Resident

Priyanka Thakur, Junior Resident

Rohit Negi, Junior Resident

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