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## A prospective interventional study of 50 patients to assess the effectiveness and safety of intralesional reconstituted bacille calmette guerin immunotherapy in treatment of warts

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### Abstract

**Introduction:** Warts are benign tumours caused by human papilloma viruses (HPV) with over 100 genotypes known till now. They are recalcitrant to treatment and prone for recurrences. Majority of the conventional treatment modalities are destructive, painful and have a greater down-time.

**Aims:** To evaluate the effectiveness and safety of intra-lesional BCG (bacille calmette guerin) immunotherapy in treatment of recalcitrant warts in immunocompetent patients.

**Materials and methods:** After an informed written consent and routine investigations, 0.1 ml of reconstituted BCG vaccine was injected into the oldest and the largest wart. Patients were evaluated every 2 weeks and were followed up for a period of 6 months. A grading scale was used to assess the response.

**Statistical analysis used:** The results obtained were statistically analysed and Z test was applied to calculate the significance of the visible difference between palmoplantar warts and common warts.

**Results:** 46 out of 50 patients completed the study. 80.43% patients (37/46) had multiple warts. 86.66% patients of palmoplantar warts (26/30) showed complete resolution of warts at the end of 6 weeks, 13.33% patients (4/30) showed partial response and none of the patients in this group were non-responders. 60% patients (6/10) of common warts showed complete response and 40% patients (4/10) were non-responders in this group. All the patients (n=4) of periungual warts showed 100% clearance at 3 months. Pain at the injection site (100%<sup>[46]</sup>), erythema (78.26%<sup>[36]</sup>), fever (76.08%<sup>[35]</sup>) and secondary infection (2.17%<sup>[1]</sup>) were the main adverse events noted.

**Conclusion:** BCG immunotherapy is a cheap, safe, effective and easily available therapeutic option which can be easily used in day to day practice.

**Keywords:** Immunotherapy, Bacille calmette Guerin, warts

### 1. Introduction

Warts are common benign proliferation of the skin and mucosa caused by human papillomavirus (HPV) infection. Human papilloma viruses (HPV) are non-enveloped viruses with icosahedral symmetry having circular double stranded DNA (ds-DNA)<sup>[1]</sup>. More than 100 HPV subtypes have been sequenced<sup>[2]</sup>, giving rise to a various presentations like common warts, palmoplantar warts, filiform warts, plane warts, mucosal warts and even the rare inherited disorder epidermodysplasia verruciformis.

The mode of transmission of HPV is mainly by contact either direct or indirect. It infects the basal keratinocytes by getting inoculated inside through a breach in the continuity of skin or mucosa. Individuals with impaired cell-mediated immunity are more predisposed<sup>[3]</sup>.

The paucity of curative treatment modality for viral warts has led to lot of research and studies in this field in recent times. The conventional modalities of treatment available are salicylic acid, podophyllin, bleomycin, 5-fluorouracil, interferons, imiquimod, cauterization, cryosurgery, laser therapy, and surgical excision.

Immunotherapy is advantageous over conventional modalities of treatment because it stimulates the immunity by mounting delayed type hypersensitivity reaction to various antigens and also to the wart tissue, thereby treating even the distant warts. It stimulates Th1 cytokines which activate NK cells,

macrophages and B- and T-lymphocytes leading to resolution of warts [4]. This study aimed to evaluate the effectiveness and safety of intra-lesional Bacille Calmette Guerin(BCG) immunotherapy in treatment of recalcitrant warts in immunocompetent patients.

**2. Materials and methods:** A prospective open labelled study comprising of 50 patients in the age group 18-65 years with different types of warts (excluding genital and verruca plana) was conducted in the department of dermatology after taking institutional ethics committee clearance. Exclusion criteria included pregnant, lactating, immunosuppressed patients, patients with ulcerated or inflamed warts, verruca plana and patients having genital and facial warts.

Patients were fully assessed to rule out any other infectious conditions before therapy and were enrolled. The target wart (oldest and the largest wart) was injected using a built-in needle insulin syringe intralesionally with 0.1 ml of reconstituted BCG. The patients were closely evaluated clinically and photographically every 2 weeks for percentage reduction in the size and number of warts, any immediate or late adverse effects or recurrence. Patients were followed up for a period of 6 months. Resolution of warts within a period of 3 months after procedure was considered successful. Response was graded as follows:

- **Responders:** ≥25 % reduction in size within a period of 12 weeks
- **Completeresponders-**100% clearance of warts within a period of 12 weeks

- Partial responders
  - A.75-99%
  - B.50-74%
  - C.25-49%
  - **Non-responders:**< 25% reduction in size at 12 weeks
- The results obtained were statistically analysed and Z test was applied to calculate the significance of the visible difference between palmoplantar warts and common warts.

**3. Results:** Forty six out of fifty patients completed the study with a mean age of 23.70 +/- 8.43 years and male to female ratio of 1.5:1. 80.43% patients (37/46) had multiple warts. 86.66% patients of palmoplantar warts (26/30) showed complete resolution of warts at the end of 6 weeks, 13.33% patients (4/30) showed partial response and none of the patients in this group were non-responders. 60% patients (6/10) of common warts showed complete response and 40% patients (4/10) were non-responders in this group. Z value was 0.47 suggesting that visible difference in the effect of BCG in these two groups was not significant. All the patients (n=4) of periungual warts showed 100% clearance at 3 months. Only 2.1% patients of common wart (1/46) came with recurrence at the end of 5<sup>th</sup> month. [Table 1]. The mean duration to achieve complete response after a single intralesional BCG injection was 6.14 +/- 2.03 weeks. The treatment was well tolerated. Pain at the injection site (100% [46]), erythema (78.26% [36]), fever (76.08% [35]) and secondary infection (2.17% [1]) were the main adverse events noted.

Table 1

	Responders				Total	Non responders No response group
	Complete response group	Partial response group				
	100%	A(75-99%)	B(50-74%)	C(25-49%)		<25%
PPW(30)	26	2	1	1	-	-
CW(12)	6	1	-	1	-	4 <sup>#</sup>
PW(4)	4	-	-	-	-	-
Total No of patients(46)	36 (78.26%)	3 (6.52%)	1 (2.17%)	2 (4.35%)	42 (91.3%)	4 (8.70%)
Recurrences				1-CW	1 (2.1%)	

PPW-Palmo plantar warts, CW- Common warts, PW-Periungual warts, #Z value = 0.47



Fig 1: A-Pre-treatment B-Complete resolution after 2 months



**Fig 2:** A- Pre-treatment B-After 6 weeks



**Fig 3:** A- Pre-treatment B- After 5 weeks



**Fig 4:** A- Pre-treatment B- Complete clearance of periungual warts after 4 weeks



**Fig 5:** A- Pre-treatment B- Complete resolution of planter warts after 6 weeks

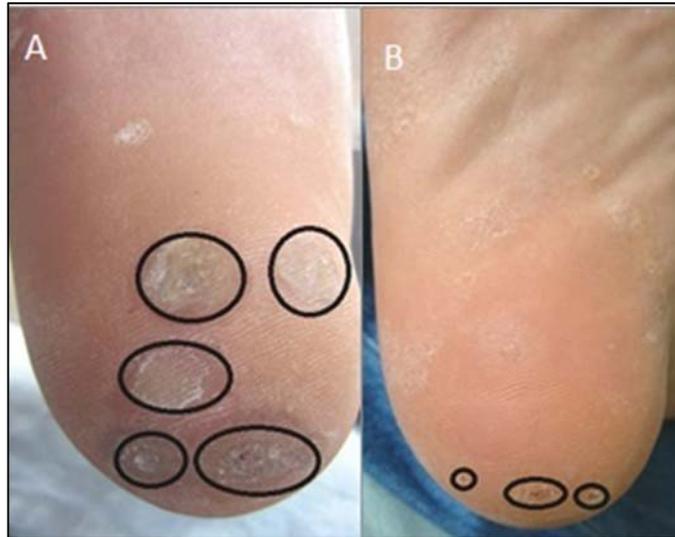


Fig 6: A- Pre-treatment B-After 5 weeks

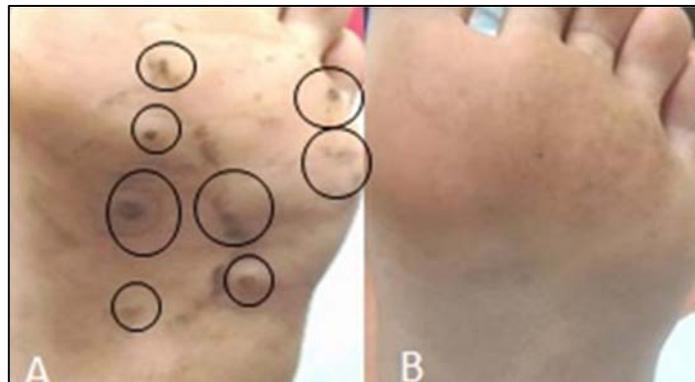


Fig 7: A- Pre-treatment B- After 7 weeks

#### 4. Conclusion

The reconstituted BCG immunotherapy is a cheap, safe, effective and easily available therapeutic option which can easily accommodated in day to day practice.

#### 5. Discussion

Plethora of therapies including CO2 fractional laser is available to us, but treatment of warts still remains challenging for a subset of patients. Still no single therapeutic option is completely successful in treating warts and preventing recurrences.

This study was conducted to study and evaluate the safety and efficacy of intralesional BCG vaccine in patients of multiple warts. Our study showed excellent therapeutic response in 78.26% patients and partial response in 13.04% patients after a mean duration of 6.14 +/- 2.03 weeks with minimal side effects. Only one patient came with recurrence of warts after 5 months.

Various immunotherapies like diphenylcyclopropanone (DCP), squaric acid dibutyl ester (SADBE), imiquimod, interferon alpha and gamma (IFN-gamma), skin test antigens like Candida, mumps, trichophyton and tuberculin, vaccines like Bacillus Calmette-Guérin (BCG) vaccine [6], mumps measles rubella vaccine [4], Mycobacterium w vaccine and autologous vaccine have been tried by different study groups with varying results.

DCP and SADBE have side-effects like allergic contact dermatitis, urticarial reactions and pigmentary disturbances. So, they are not used much. Autologous vaccine therapy is limited by the malignant potential of the virus.

BCG vaccine is a live attenuated vaccine derived from Mycobacterium bovis and is well known for its prophylactic effect against tuberculosis. It stimulates the delayed type hypersensitivity reaction and increases the recruitment of various immune cells like NK cells, macrophages, lymphocytes resulting in resolution of viral warts.

In a study by Mohammed Z. Kenawi *et al* [5], 39.3% patients showed complete clearance after third session of intralesional BCG. Similarly, Sharquie *et al* [6], used BCG vaccine for treatment of warts and found that 40% achieved complete response after the third session.

According to the study by Saini *et al* [7], intralesional MMR vaccine was used and complete therapeutic response was seen in 46.5% patients with a 2.41 ± 0.68 mean number of intralesional injections and the mean duration of 7.15 ± 2.07 weeks.

A study done by Horn *et al* [8]. Using intralesional injection of Candida, mumps, or trichophyton skin test antigens showed good clearance rates (54%) and distant response rates in subjects receiving antigen. They compared the efficacy of skin test antigens (mumps, candida, and trichophyton), IFN α-2b and placebo injection in a randomized controlled trial. More than 75% clinical

resolution was seen in 54% of the patients injected with antigen alone and 68% of patients injected with antigen plus interferon.

The clearance rate of warts with various immunotherapies other than BCG vaccine ranged from 39.7 to 87%. Hence, the clearance rate of warts using BCG was comparable to other skin test antigens and vaccines for the treatment of warts. Still larger controlled studies are needed to evaluate the safety and efficacy of various immunotherapies.

## 6. Acknowledgements: Nil

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