

The *Bacillus Calmette-Guérin* (BCG) Vaccine Is it a better choice for the treatment of viral warts?

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لقاح عصية كالميت-غيران هل هو خيار أمثل لعلاج الثآليل الفيروسية؟

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ABSTRACT: Objectives: This study aimed to compare the effectiveness of the *bacillus* Calmette-Guérin (BCG) vaccine with topical salicylic acid (SA) in the treatment of viral warts. **Methods:** This non-randomised controlled trial was conducted at the Al-Sader Teaching Hospital, Basrah, Iraq, from January 2016 to April 2017. A total of 201 patients with viral warts were injected with an intradermal purified protein derivative. Subsequently, those with negative tuberculin test results received an intradermal BCG vaccination, while those with positive results underwent conventional treatment with topical SA. Patients were assessed for any signs of improvement at one, two and three months. **Results:** Overall, 190 patients completed the trial; of these, 133 (70%) received the BCG vaccine and 57 (30%) were treated with topical SA. Complete response to treatment was observed in 9.8% and 5.3% of patients in the BCG and SA groups, respectively ($P < 0.001$). Cure rates were significantly higher for patients with genital (22.2% versus 7.7%; $P = 0.002$) and common warts (8.5% versus 0%; $P = 0.001$) treated with the BCG vaccine; however, the reverse was true for flat warts (12.9% versus 25%; $P = 0.041$). A binary logistic regression analysis indicated that BCG therapy was the only significant independent predictor of positive treatment response (odds ratio: 7.56, 95% confidence interval: 3.72–15.36; $P < 0.001$). **Conclusion:** The BCG vaccine was more effective than topical SA for treating viral warts, with the best response noted in the treatment of genital warts, followed by flat warts. However, *plantar* warts demonstrated least response to this treatment.

Keywords: Human Papilloma Viruses; Warts; Immunotherapy; BCG Vaccine; Salicylic Acid; Clinical Trial; Treatment Effectiveness.

المخلص: الهدف: هدفت هذه الدراسة إلى مقارنة فعالية لقاح عصية كالميت-غيران (BCG) مع حمض الساليسيليك الموضعي (SA) في علاج الثآليل الفيروسية. **الطريقة:** أجريت هذه التجربة غير العشوائية ذات الضوابط في مستشفى الصدر التعليمي بالبصرة في العراق، من يناير 2016 إلى أبريل 2017. تم حقن ما مجموعه 201 مريضاً مصاباً بالثآليل الفيروسية بمشتق البروتين المنقى داخل الجلد، بعد ذلك، تلقى أولئك الذين ظهرت نتائجهم سلبية لقاح BCG داخل الجلد، في حين خضع أولئك الذين كانت نتائجهم إيجابية للعلاج المعتاد باستخدام SA الموضعي. تم تقييم المرضى لأي علامات تحسن بعد فترات شهرين وثلاثة أشهر. **النتائج:** أكمل 190 مريضاً التجربة منهم 133 مريضاً (70%) تلقوا لقاح BCG وعولج 57 (30%) منهم باستخدام SA الموضعي. وقد لوحظ أن هناك استجابة كاملة للعلاج في 9.8% و 5.3% من المرضى في مجموعتي BCG و SA على التوالي ويفارق معتمد به احصائياً ($P < 0.001$). وكانت معدلات الشفاء أعلى بكثير للمرضى الذين كانوا يعانون من ثآليل الأعضاء التناسلية (22.2% مقابل 7.7%; $P = 0.002$) والثآليل الشائعة (8.5% مقابل 0%; $P = 0.001$) للذين عولجوا بلقاح BCG؛ في المقابل، كان العكس صحيحاً بالنسبة للثآليل المسطحة (12.9% مقابل 25%; $P = 0.041$) كما أشار تحليل الانحدار اللوجستي الثنائي إلى أن علاج BCG كان المتنبئ المستقل الوحيد المهم للاستجابة العلاجية الإيجابية (نسبة الأرجحية: 7.56، فاصل الثقة 95%: 3.72–15.36; $P < 0.001$). **الخلاصة:** كان لقاح BCG أكثر فعالية من SA الموضعي في علاج الثآليل الفيروسية، مع ملاحظة أن الإستجابة كانت أفضل في علاج الثآليل التناسلية، تليها الثآليل المسطحة بينما أظهرت الثآليل الأخمصية أقل استجابة لهذا العلاج.

الكلمات المفتاحية: فيروسات الورم الحليمي البشري؛ البثور؛ العلاج المناعي؛ لقاح عصية كالميت غورين؛ حمض الساليسيليك؛ تجربة سريرية؛ فعالية العلاج.

ADVANCES IN KNOWLEDGE

- The treatment of viral warts is challenging, with some warts resistant to conventional therapy; however, immunotherapy is a relatively new yet promising modality, particularly the *bacillus Calmette-Guérin* (BCG) vaccine.
- Results from this non-randomised controlled trial indicate that immunotherapy with the BCG vaccine was more effective than conventional treatment using topical salicylic acid.

APPLICATION TO PATIENT CARE

- The results of this trial highlight the effectiveness of the BCG vaccine as an alternative treatment for viral warts. This modality can be simply and cheaply implemented into clinical practice.

VIRAL WARTS ARE COMMON BENIGN SKIN growths caused by human papilloma virus (HPV) infections.¹ Diverse HPV strains are responsible for specific types of warts, such as common, flat, intermediate, *plantar*, mosaic, anogenital and oral warts.² In general, warts predominantly affect children compared to infants and adults and more frequently affect the face and upper and lower limbs.^{1,3,4} Viral warts can proliferate and increase in both dimension and quantity; on the other hand, spontaneous remission within a two-year period has also been reported.^{4,5} In addition, viral warts often recur and are unresponsive to conventional management.^{4,6} As such, the prognosis of individual cases is usually uncertain.

Various modalities exist in the treatment of viral warts, including surgical excision, electrocauterisation, cryotherapy and laser ablation; however, these options are often time-consuming, painful and potentially disfiguring.⁴ Topical salicylic acid (SA), although usually readily available and a convenient method of treating warts at the *focus* location, can be irritating and is inefficient in cases with numerous warts or warts in several sites; moreover, patients must adhere to a strict daily application schedule for the treatment to be effective.^{7,8} Optimally, the goal of treatment is to eliminate the warts with no subsequent recurrence (i.e. lifelong immunity) and without disfiguring the patient; however, no single therapy is currently guaranteed to cure viral warts and prevent their recurrence.⁵ This has made treatment somewhat of a challenge for both dermatologists and patients.

Immunotherapy represents a promising new modality for the management of recurring and resistant viral warts.^{9–11} This method can resolve warts without physically altering or damaging the surrounding tissue; moreover, it enhances the host response against the causal agent, leading to widespread resolution and diminishing the likelihood of recurrence.^{6,7} Although the exact mechanism of its action in treating viral warts is not yet completely understood, immunotherapy is believed to stimulate a systemic T cell-mediated response resulting in resolution both at the site of contact and distally.^{12,13} The objective of this study was to compare the effectiveness and safety of the *bacillus* Calmette-Guérin (BCG) vaccine as a form of immunotherapy in comparison to conventional topical SA application for the treatment of viral warts.

Methods

This non-randomised controlled trial was carried out from January 2016 to April 2017 at the dermatology outpatient clinic of the Al-Sader Teaching Hospital in Basrah, Iraq. All consecutive patients attending

the clinic during this period with more than five clinically-diagnosed viral warts were included in the trial. However, immunosuppressed patients and those with chronic diseases such as diabetes mellitus, vitiligo and *lupus* or local or systemic inflammation were excluded, as were pregnant or lactating women. None of the participants had received any recorded treatment for warts within the three-month period preceding the start of the trial.

Interviews were conducted to collect information regarding the patients' age, gender and duration of warts; in addition, a clinical examination was conducted to determine the type, site and number of warts. Subsequently, each patient underwent a Mantoux tuberculin skin test in which 0.1 mL of purified protein derivative was injected intradermally into the left forearm at the *volar* aspect. Approximately 48–72 hours later, a trained researcher inspected and palpated the skin to determine the presence or absence of an induration. In order to standardise the results of the test, the diameter of the induration was measured to determine the presence (i.e. induration of ≥ 15 mm) or absence (i.e. induration of < 15 mm) of cell-mediated immunity to tuberculin.¹⁴ Based on this, patients were assigned to either the BCG group if they had negative results or the SA group if they had positive results. The former received one intradermal dose of the BCG vaccine while the latter underwent conventional treatment involving the daily application of 15–20% SA in a suitable base.

Subsequently, patients in both groups were followed-up for three months. Clinical evaluation and photographic measurement of the lesions were performed at baseline before treatment and at one, two and three months after treatment. Based on these indicators, response to treatment was calculated as either a complete response to treatment (defined as the total resolution of all warts), partial response (defined as a decrease in the number and/or apparent size of the warts), mild response (defined as a $< 25\%$ resolution in the number and/or apparent size of the warts) or no response (defined as no decrease in the number and/or apparent size of the warts).

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), Version 20.0 (IBM Corp, Armonk, New York, USA). The results were reported using descriptive statistics. Quantitative results were presented as means and standard deviations while nominal results were presented as percentages and frequencies. Differences were assessed using Chi-squared or Fisher's exact tests, wherever applicable. Non-parametric Mann-Whitney-U, t test and analysis of variance tests were performed to compare the means of independent variables. A

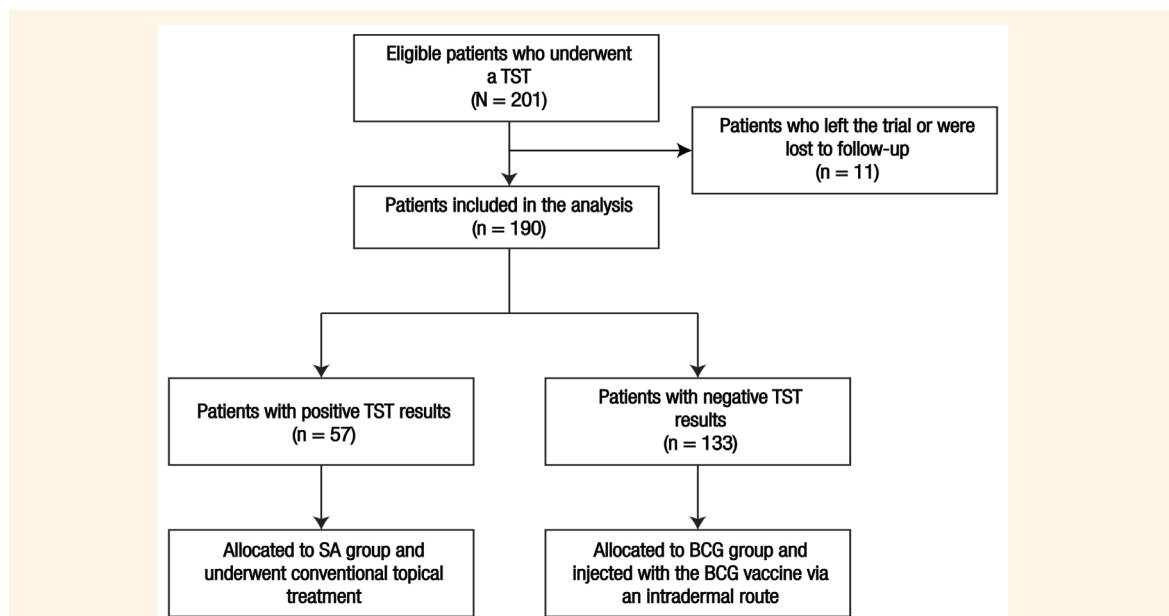


Figure 1: Flowchart showing the group allocation and intervention processes applied to the clinical trial.

TST = tuberculin skin test; SA = salicylic acid; BCG = bacillus Calmette-Guérin.

binary logistic regression analysis was conducted to determine independent factors predicting response to treatment. For the purposes of the regression analysis, response to treatment was dichotomised into either a positive response (i.e. complete or partial response to treatment) or no response. A *P* value of <0.050 was considered to be statistically significant.

This study was approved by the Ethical Committee of the College of Medicine, University of Basrah [Code 030407042-2016]. Informed written consent was obtained from all participants.

Results

A total of 201 patients were originally enrolled in the trial; however, five received only the tuberculin

injection and another six were lost to follow-up, resulting in a final sample of 190 patients (94.5%). Of these, 129 (67.9%) were male and 61(32.1%) were female (ratio: 2.1:1). The mean age was 27.8±8.7 years and mean number and duration of viral warts was 20.9 ± 7.3 warts and 9.0±3.7 months, respectively. The face was the most common site affected (30.5%), followed by the hands (23.7%), upper & lower limbs (20.6%), genitalia (14.7%), and neck (2.6%). Multiple sites were involved in 7.9% of cases. In terms of wart type, 43.2% presented with common warts, while 20.5% had flat warts, 16.3% had genital warts, 11.6% had *filiform* warts and only 8.4% had *plantar* warts.

Based on the results of the Mantoux test, 133 patients (70%) received the BCG vaccine, while the remaining 57 patients (30%) received conventional

Table1: Comparison of treatment response to the *bacillus* Calmette-Guérin vaccine or conventional treatment with salicylic acid among patients with viral warts (N = 190)

Type of wart	Response, n (%)						P value
	BCG group* (n =133)			SA group+(n =57)			
	Complete	Partial	None	Complete	Partial	None	
Common	5 (8.5)	45 (76.3)	9 (15.3)	0 (0)	4 (17.4)	19 (82.6)	0.001
Flat	4 (12.9)	26 (83.9)	1 (3.2)	2 (25)	4 (50.0)	2 (25)	0.041
Genital	4 (22.2)	13 (72.2)	1 (5.6)	1 (7.7)	4 (30.8)	8 (61.5)	0.002
Filiform	0 (0)	12 (80)	3 (20)	0 (0)	4 (57.1)	3 (42.9)	0.334
Plantar	0 (0)	4 (40)	6 (60)	0 (0)	4 (66.7)	2 (33.3)	0.608
Total	13 (9.8)	100 (75.2)	20 (15)	3 (5.3)	20 (35.1)	34 (59.6)	<0.001

BCG= bacillus Calmette-Guérin; SA = salicylic acid.

$\chi^2 = 25.387; P = 0.002.$ $\chi^2 = 17.944; P = 0.019.$

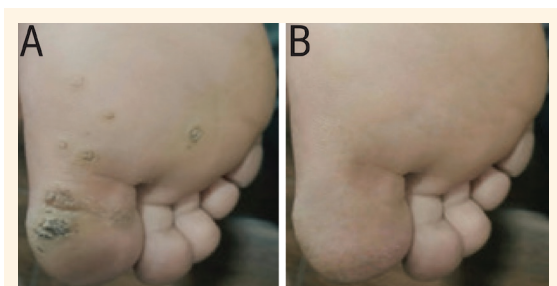


Figure 2: Photographs of the foot sole and toes of a patient showing (A) multiple *plantar* warts before treatment and (B) complete clearance two months after receiving the *bacillus Calmette-Guérin* vaccine.

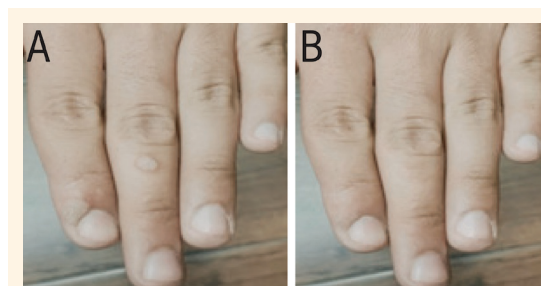


Figure 3: Photographs of the fingers of a patient showing (A) common warts before treatment and (B) complete clearance two months after receiving the *bacillus Calmette-Guérin* vaccine.

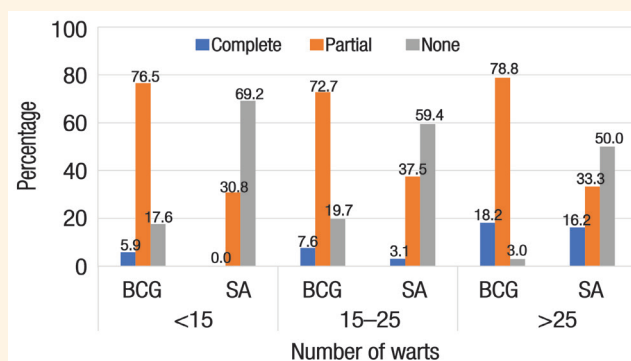


Figure 4: Comparison of treatment response to the *bacillus Calmette-Guérin* vaccine or conventional treatment with salicylic acid according to number of warts among patients with viral warts (N = 190). The difference between groups was statistically significant ($P = 0.043$).

BCG= *bacillus Calmette-Guérin*; SA= *salicylic acid*.

Table 2: Literature review of previous studies assessing use of the *bacillus Calmette-Guérin* vaccine for the treatment of viral warts^{12,16,22-24}

Author and year of study	Mode of administration	Duration of follow-up	Number of sessions	Interval between sessions	CC rate	Side-effects
Sharquie <i>et al.</i> ¹² (2008)	Intradermal	3 months after the last dose	3	4 weeks	39.7%	•None
Kenawi <i>et al.</i> ²² (2012)	Intralesional	Until CC or up to four treatment sessions	4	3 weeks	40%	•Pain, ulcers and constitutional symptoms (i.e. fever, necrosis and lymphadenitis)
Podder <i>et al.</i> ¹⁶ (2017)	Intradermal	4 weeks after treatment	3	4 weeks	48.5%	•Pain during the injection and abscess formation and scarring at the injection site
Rajashekar <i>et al.</i> ²³ (2018)	Intralesional	6 months	4	2 weeks	30.8%	• Pain, fever, <i>myalgia</i> and flu-like symptoms
Jaisinghani <i>et al.</i> ²⁴ (2019)	Intralesional	3 months	3	3 weeks	73.53%	• Pain, flu-like symptoms, erythema, oedema and BCGitis
Present study (2020)	Intradermal	3 months	1	-	9.8%	• Minimal scarring at the injection site

CC = complete clearance; BCG = *bacillus Calmette-Guérin*

treatment with topical SA [Figure 1]. The overall cure rate was significantly higher among those who received the BCG vaccine compared to those receiving conventional treatment (9.8% versus 5.3%; $P < 0.001$).

Moreover, in the BCG group, rates of partial response and non-response to treatment were 75.2% and 15%, respectively, compared to 35.1% and 59.6% in the SA group. In terms of wart type, complete clearance was

more frequently observed with BCG therapy among those with common warts (8.5% versus 0%; $P = 0.001$) and genital warts (22.2% versus 7.7%; $P = 0.002$), while the reverse was true for flat warts (12.9% versus 25%; $P = 0.041$) [Table 1].

In both groups, patients most frequently started responding to treatment by the second month [Figures 2 and 3], with a significantly greater response observed in the BCG group compared to the SA group (10.5% versus 1.8%; $P = 0.042$). By the third month, 84.9% of the BCG group were partially or completely cured in comparison to 40.4% of the SA group ($P < 0.001$). Moreover, while the rate of response to treatment increased alongside the number of warts in both groups, the response was significantly greater in the BCG group ($P = 0.043$) [Figure 4]. Although the cure rate was higher among those with longer disease durations (≥ 10 months) compared to those with shorter durations (< 10 months), this difference was not statistically significant (11.9% versus 8.8%; $P = 0.451$).

The binary logistic regression analysis showed that BCG therapy was the only significant independent determinant of response to treatment (odds ratio: 7.56, 95% confidence interval: 3.72–15.36; $P < 0.001$). All other variables were non-significant, including age, gender and the number, site, type and duration of the warts. In terms of possible complications from treatment, no side-effects were documented in any of the patients regardless of group, except for mild scarring due to the intradermal injection of the vaccine in the BCG group.

Discussion

Immunotherapies can be administered via topical, intralesional or systemic routes, with systemic immunotherapy found to be a safe, affordable and effective option for multiple intractable viral warts.^{4,9,15} Originally, the BCG vaccine was formulated as a prophylactic against tuberculosis; however, this immunotherapy has since been incorporated in the management of other diseases with varying success rates, including malignant melanomas, alopecia *areata* and transitional cell carcinomas.^{16–19} The BCG vaccine affects the immune system and offers protection against infections—including those viral in origin—via the stimulation of innate immune memory and activation of the heterologous lymphocytes, resulting in enhanced cytokine production.²⁰

The current clinical trial aimed to compare two methods of treating viral warts—the BCG vaccine as a form of immunotherapy and conventional treatment with topical SA—in terms of both effectiveness (i.e.

response to treatment) and safety (i.e. the occurrence of any medical complications). The BCG vaccine was found to result in a significantly higher rate of complete response to treatment compared to topical SA (9.8% versus 5.3%). This is potentially because immunotherapy is more effective at destroying the infected cells by activating a systemic inflammatory response; in addition, it removes any potential issue of non-adherence to treatment as the vaccine is injected by clinicians, while topical treatment is carried out by the patients themselves.²¹ In Iraq, the BCG vaccine is provided to all citizens free of charge at primary health centres; as such, it is an excellent option for low-income patients.

Nevertheless, other studies have reported much higher rates of complete clearance with BCG therapy (39.7–40%).^{12,22} Variations in specific treatment details might play a role in the rate of complete clearance [Table 2].^{12,16,22–24} The low rate in the present study could be due to the shorter duration of follow-up (three months) or the fact that patients received only one BCG injection via an intradermal route; it is possible that some of the partial responses would have cleared completely with more time, alternative routes or additional BCG injections. Rajashekar *et al.* observed a clearance rate of 30.8% with multiple intralesional BCG injections and a longer duration of follow-up (six months).²³ Another study noted a clearance rate of 73.53% using three doses of intralesional BCG vaccine.²⁴ Both the intralesional administration and the increased number of doses might explain such high clearance rates, considering that drug effect is a function of both dose and time.²⁵ Indeed, repeated BCG injections seem to result in a booster effect or dose-response relationship.^{23,24}

In the current study, treatment response was found to be linked to greater numbers of warts with both types of therapy, although better responses were noted in the group receiving the BCG vaccine. This is in agreement with results reported by Kenawi *et al.*²² These findings could be explained by the fact that patients with larger numbers of warts in the SA group might be less likely to comply with a treatment regimen which involved the daily topical application of SA on each individual wart over a 12-week period; in contrast, BCG therapy is much more convenient for the patient as it simply involves a single injection performed by a clinician and results in the clearance of warts from multiple sites.

Regardless of type of treatment, the best responses in the present study were noted for genital and flat warts, with *plantar* warts demonstrating the least response. Similar results have been reported by other researchers.^{12,26,27} Genital warts are typically

caused by HPV types 6 and 11 which have a low risk of inducing intraepithelial dysplasia; this could potentially explain better responses to BCG treatment for these types of warts.²⁸ In contrast, Youn *et al.* reported that *plantar* warts exhibited superior cure rates with liquid nitrogen cryotherapy compared to other types of warts; the authors attributed this to the effectiveness of routine paring (i.e. the elimination of excessive keratin) before each cryotherapy session.²⁹

Generally, patients in both groups in the current study began exhibiting responses to treatment after two months. Podder *et al.* similarly reported that clinical results first became apparent four weeks after BCG therapy was initiated.¹⁶ Moreover, while the difference was not statistically significant, cases with longer disease duration in the present study appeared to exhibit better responses to BCG therapy, but not SA treatment. This result is consistent with those obtained by Kenawi *et al.*²² Patients with persistent viral warts may demonstrate better enhancement and stimulation of immune response with BCG therapy, in which case maintaining a healthy immune status could prevent recurrence.²⁹ In contrast, Bruggink *et al.* and Choi *et al.* concluded that longer-lasting warts were more difficult to treat with either conventional treatments alone (i.e. liquid nitrogen and topical SA) or combined with an immunomodulator (dinitrochlorobenzene), which they also assumed to be due to an immunity-related issue.^{8,21}

In the current study, patients with negative Mantoux test results were given the BCG vaccine to prove its ability to reactivate immunity and, consequently, its potential role in the treatment of viral warts. Prior to their assignment to the BCG or SA groups, all patients in the current trial underwent tuberculin skin tests on the assumption that a positive Mantoux test would measure the degree of hypersensitivity to tuberculin.¹⁴ However, the absence of an induration (or one under 15 mm in diameter) may be due to the lack of previous sensitisation; moreover, positive results may indicate intact or persistent cell-mediated immunity, while negative results could indicate a weakened immune system due to a myriad of reasons, such as a concurrent viral infection.^{14,30}

The study was subject to certain limitations. First, the lack of randomisation in the allocation of treatment groups could have resulted in potential confounding bias, restricting complete confirmation of the causal effect of each treatment. However, such confounding was adjusted for by applying multiple regression analyses.³¹ Another limitation was that the precise cytokine levels of the patients in the BCG group were not measured due to financial reasons.

Finally, although the diameter of the induration in each patient was measured after the tuberculin skin test, false-negative results could not be excluded.^{14,30}

Conclusion

Topical SA is widely used as treatment modality in the management of cutaneous viral warts. However, the results of this clinical trial provide evidence to support the efficacy of intradermal BCG therapy over this conventional treatment, particularly for common and genital warts. However, further randomised controlled studies are necessary to support these findings and more clearly ascertain the effectiveness of BCG therapy in the treatment of viral warts.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

FUNDING

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