Bacille Calmette-Guerin immunotherapy of viral warts

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ABSTRACT

الأهداف: بيان مدى فعالية اللقاح (BCG) في علاج مرض الثآليل الجلدية (الشائعة،المسطحة و ثآليل باطن القدم) عن طريق الغرز الجلدي.

الطريقة: تمت الدراسة في قسم الأمراض الجلدية و الزهرية في العيادة الاستشارية في مستشفى بغداد التعليمي للفترة من الأول من آذار 2005م و لغاية الأول من حزيران 2006م. تم أخذ التاريخ المرضي لمائتين من الأشخاص المصابين بمرض الثآليل الجلدية (الشائعة، المسطحة، ثآليل باطن القدم) وتم فحصهم سريراً مع التأكيد على عدم استخدام أي نوع من العلاجات الموضعية والفموية فترة ثلاثة أشهر قبل بدء الدراسة وقُسم المرضى إلى مجموعتين متساويتين في العدد و متطابقتين في العمر و الجنس و في فترة بقاء المرض. تم علاج المجموعة الأولى باللقاح (BCG) و بجرعة مقدارها 0.1ml في المرة الواحدة عن طريق الغرز الجلدي في أعلى الذراع، وكحد أعلى ثلاث جرع بين الجرعة ولاحقتها فترة لا تقل عن الشهر. قورنت النتائج مع المجموعة الضابطة باستخدام الماء المقطر و بنفس الطريقة، تم معاينة المرضى كل أسبوعين لغرض ملاحظة الاستجابة الجزئية أو الكلية والتأكد من ظهور أية أعراض جانبية، فترة المتابعة استمرت لثلاثة أشهر بعد آخر جرعة.

النتائج: أكمل الدراسة واحد و ثمانين مريضا فقط من المجموعة الأولى و ثلاث و سبعون مريضا فقط من المجموعة الثانية. أظهرت النتائج أن 30 مريضا (39.7%) من اللذين تم علاجهم باللقاح (BCG) أظهروا شفاءً كاملاً، 6 مرضى (6.4%) بعد الجرعة الأولى، 15 مريضاً (18.3%) بعد الجرعة الثانية و9 مرضى (15.0%) بعد الجرعة الثالثة. هذه النتائج ذات أهمية إحصائية بالمقارنة مع الماء المقطر القيمة الاحتمالية ($p<0.05$) حيث أظهر 10مرضى فقط (13.67%) شفاءً كاملا بعد إكمالهم فترة العلاج. تم متابعة المرضى الذين أظهروا شفاءً لمدة ثلاثة أشهر (مرة كل أسبوعين) بعد أخر جرعة من العلاج فلم تسجل عودة للثآليل في أي مريض. عند معالجة الحالات التي لم تستجب للعلاج بالماء المقطر باستخدام اللقاح (BCG) فأن نسبة الاستجابة كانت (42.7%) من مجموع المرضى ،لم يلاحظ ظهور أعراض جانبية موضعية أو جهازية عدا الاستجابة الطبيعية في موضع غرز اللقاح(BCG).

خاتمة: يمكن اعتبار اللقاح (BCG) علاج جديد و فعال و أمين لعلاج الثآليل الجلدية.

Objective: To assess the effectiveness of the Bacille Calmette-Guérin (BCG) vaccine in the treatment of viral warts.

Methods: A single blind placebo controlled study conducted at the Department of Dermatology, Baghdad Teaching Hospital, Baghdad, Iraq from March 2005 to June 2006. Two hundred patients with viral warts were enrolled in this study, and were fully assessed before therapy. The patients were divided into 2 equal matched groups. Group 1 was designed as the treatment group and received BCG vaccine in 1-3 doses with a one-month interval, while group 2 was injected with distilled water. The patients were evaluated every 2 weeks for evidence of regression of lesions. The follow up period lasted for 3 months after the last dose.

Results: A total of 154 patients completed the study: 81 patients in group I and 73 patients in group II. Thirty (39.7%) patients out of 81 patients in group I showed complete recovery. These results were significantly high ($p<0.05$) when compared with total response, 10 (13.7%) out of 73 patients in group II. No recurrence has been reported during the follow up period. When cases that failed to respond to placebo were treated with BCG in a similar manner to group I, there was total response in 15 (42.7%) out of 44 patients. No side effects were observed.

Conclusions: The BCG vaccine was an effective and safe modality of treatment of viral warts.

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Viral warts are common dermatological diseases caused by human papilloma virus (HPV). Although spontaneous recovery is high, it usually takes a long time, even years, and some patients may not show this spontaneous healing with long term follow up.[1,2] There are many modalities of therapy, such as electrocautery, chemicocautery, cryotherapy, and others, most of these take months, and many of them are destructive and might cause scarring, and the recurrence rate after these modalities of therapy may be high. The existence of multiple treatment modalities reflects the fact that none is uniformly effective or directly antiviral.[1] Bacille-Calmette-Guérin (BCG) was introduced as a prophylactic agent against tuberculosis, accidentally it has been found that the leprosy incidence has decreased tremendously.[3] The BCG also had been used in the treatment of malignant melanoma,[4] transitional cell carcinoma of the bladder,[5] in alopecia areata,[6] and recurrent oral aphthosis.[7] The mechanism of action could be explained on the basis of stimulating macrophages, T and B lymphocytes, natural killer cells function that might help in resolution of the viral warts.[6-9] The percentage of skin disease among BCG vaccinated individuals was significantly lower compared with healthy controls, these diseases include psoriasis, fungal infection, cutaneous leishmaniasis, molluscum contagiosum, and lichen planus, indicating that BCG decreases the frequency of skin diseases.[8] The aim of this work, is to assess the efficacy and safety of the BCG vaccine in the treatment of viral warts.

Methods. A single blind, placebo controlled and prospective study was arranged to evaluate the therapeutic effectiveness of intradermal BCG in the treatment of viral warts. Two hundred patients with viral warts (common, plantar, and plane warts) were enrolled in this study from the out patients clinic at the Department of Dermatology and Venereology, Baghdad Teaching Hospital, Baghdad, Iraq from March 2005 to June 2006. All patients included in the present work had no history of any used medications during the last 3 months, were otherwise healthy with no chronic systemic illness. Patients with any chronic disease like diabetes mellitus, vitiligo, and other immunosuppressive diseases or drugs were excluded. All patients were interrogated, and a full history was taken regarding age, gender, duration of the warts, and any previous modality of treatment. The patients were examined closely to determine the clinical type of the warts, their sites, and the number of lesions, distribution and the presence of previous BCG scar. Formal consent was taken from each patient before starting therapy, after full explanation regarding: nature of disease, course, and method of treatment, duration, and follow up. Ethical approval for the study was granted by the scientific committee of the Scientific Council of Dermatology and Venereology, Iraqi Board for Medical Specifications. The patients were randomly divided into 2 groups: Group 1 was designed as the treatment group and received 0.1 ml of intradermal freeze dried glutamate BCG vaccine, (Japan BCG laboratories) reconstituted with 1 ml saline using a 30 gauge needle on a 1 ml tuberculin Luer syringe, in the upper arm in 1-3 doses with one month intervals. Group 2 was given 0.1 ml placebo intradermal distilled water in the upper arm, using a 30 gauge needle on a 1 ml tuberculin Luer syringe, in 1-3 doses with one month intervals and served as a placebo group. The patients were evaluated and examined every 2 weeks for evidence of partial or complete regression of their lesions and to record any local or systemic adverse effects. The follow up period lasted up to 3 months after the last dose.

Descriptive statistics were carried out by scientific calculator. Analytic statistics were carried out by the Statistical Package for Social Sciences version 11. Chi-square and t-test were conducted, $p<0.05$ was considered to be statistically significant.

Results. Two hundred patients with various types of viral warts were evaluated in this study. Group 1 included 44 (44%) females and 56 (56%) males. Their ages ranged from 6-45 with mean±SD of 20.6±9.4 years, while the duration ranged from 5-36 with mean±SD of 17.9±10.6 months, the number of the lesions in each patient ranged from 10-55 with mean±SD of 22.9±12.6 lesions. Eighty-eight (88%) patients had scar of previous BCG vaccination while 12 (12%) had no scar. The clinical variants of warts were common warts in 60 (60%) patients, plane warts in 26 (26%) patients, and plantar warts in 14 (14%) patients. Group 2 included 48 (48%) females and 52 (52%) males. Their ages ranged from 6-41 years with mean±SD of 21.6±7.8 years, the duration of the lesions ranged from 10-36 months with mean±SD of 17.06±7.4 months, the number of the lesions ranged from 8-48 with mean±SD of 19.7±8.8 lesions. Ninety (90%) patients had a scar from a previous BCG vaccination, while 10 (10%) patients had no scar. Clinical varieties of warts were common warts in 45 (45%) patients, plane warts in 30 (30%), patients and plantar warts in 25 (25%) patients. The response to treatment in both groups was as follows: Group 1: Out of hundred patients receiving the first BCG dose, 6 patients defaulted so only 94 patients completed the study, 6 (6.4%) showed complete disappearance of their warts and 88 (93.6%) showed no response. The non-responders to the first BCG dose were vaccinated with a second dose after one month (88 patients), 6 patients had defaulted so only 82 patients completed the study, and 15 (18.3%) patients showed complete disappearance of their warts and 67 (81.7%) showed no response. The non responders to the 2nd BCG dose were vaccinated

with a third dose after one month (67patients), 7 patients had defaulted so only 60 patients completed the study, 9 (15%) showed complete disappearance of their warts and 51 (85%) showed no response. The overall response was observed in 30 (39.7%) out of 81 patients after 1-3 doses of BCG vaccination, 19 (63.3%) patients had common warts, 7 (23.3%) patients had plane warts, and 4 (13.3%) patients had plantar warts. Twenty-eight (93.3%) patients had previous BCG scar, and only 2 (6.7%) had no scar. Fifty-one (61.3%) patients showed no response. Twenty-five (49%) patients of the non-responder showed partial regression of their warts. The sign of regression was noticed in all patients as follows: 1. Itching: was the earliest symptom and experienced by all patients (100%), and started after 7 days of treatment usually mild to moderate in intensity, but no excoriation or koebnerization was seen. It persisted until complete vanishing of the warts. 2. Increasing in size: this occurred in common and plane warts and was noticed by 24 (80%) patients after itching. This continued for 2 weeks, and then the warts gradually regressed in size until complete regression. 3. Tenderness: nine (30%) patients with common and plantar warts developed slight tenderness after one week and then they became less keratotic and in one (3.3%) patient with plantar warts, they bleed easily after a trivial trauma. There were no observed local or systemic adverse effects of intradermal BCG during treatment apart from the usual appearance of tender papule or pustule at the site of injection. These unwanted reactions were mild and transient and did not necessitate the cessation of treatment. The 30 patients who showed complete resolution of the warts were followed up regularly every 4 weeks for 12 weeks. No evidence of recurrence of warts was seen during the follow up period (**Figures 1 and 2**). Group 2: Out of hundred patients receiving the first distilled water dose, 7 defaulted so only 93 patients completed the study, only one (1.1%) patient showed complete disappearance of their warts. The non-responders to the first distilled water dose were given a second dose after one month (92 patients), 9 patients defaulted so only 83 patients completed the study, 6 (7.2%) patients showed complete disappearance of their warts, and 77 (92.8%) patients showed no response. The non-responders to the second distilled water dose were given a third dose after one month (77 patients), 11 patients defaulted so only 66 patients completed the study, 3 (4.4%) showed complete disappearance of their warts and 63 (95.6%) showed no response. The overall response was observed in 10 (13.6%) out of 73 patients after 1-3 doses of distilled water, 5 (50%) patients had common warts and 5 (50%) patients had plane wart, all of them (100%) with previous BCG scar. Sixty-three (86.4%) patients showed no response. Four (6.2%) patients of the non-responders showed partial regression of their warts. There were no observed local or systemic adverse effects. Therefore, the overall response was observed in the BCG treated group was significantly high (p=0.00043) as compared to the distilled water group. The non-responded patients, after distilled water treatment received further courses of BCG treatment for medico ethical purposes one month after the last distilled water dose in similar manner to Group I. Out of 63 patients, 19 patients had defaulted so only 44 patients completed the study, 3 (6.8%) patients showed complete disappearance of their warts and 41 (92.2%) patients showed no response. The non responders to the first BCG dose were vaccinated with a second dose after one month (41 patients), 2 patients defaulted so only 39 patients completed the study, 8 (20.5%) patients showed complete disappearance of their warts and 31 (79.5%) showed no response. The non-responders to the second BCG dose were vaccinated with a third dose after one month (31 patients), 5 patients defaulted

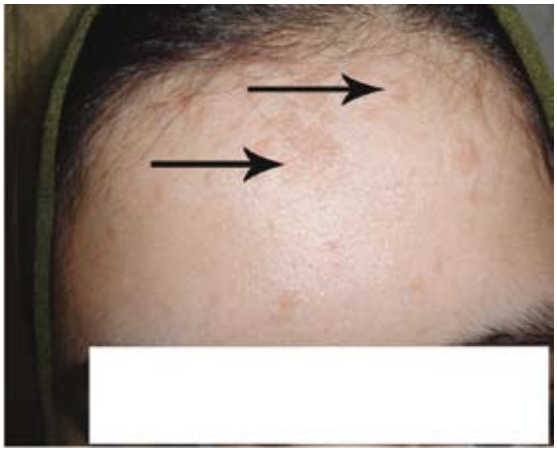

Figure 1. Plane wart in a 17-year-old female before treatment with Bacille Calmette-Guérin vaccine.

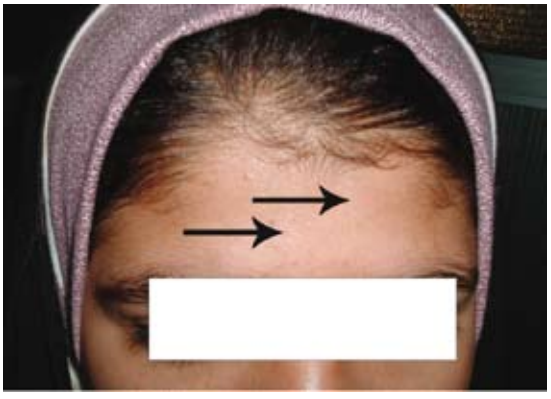

Figure 1. Plane wart in a 17-year-old female after treatment with Bacille Calmette-Guérin vaccine.

so only 26 patients completed the study, 4 (15.4%) patients showed complete disappearance of their warts and 22 (84.6%) patients showed no response. The overall response was observed in 15 (42.7%) out of 44 patients after 1-3 doses of BCG vaccination, 8 (53.3%) patients had common warts, 4 (26.7%) patients had plane warts, and 3 (20%) patients had plantar warts, all of them with previous BCG scar. Twenty-two patients (59.5%) showed no response. Ten patients (45.4%) of the non-responders show partial regression of their warts. All (100%) patients showed itching early after response, and 11 (73.3%) patients developed an increase in the size of their warts. No unwanted reactions were observed, and no evidence of recurrence of warts was seen during the follow up period. Therefore, the overall response was observed after BCG vaccination was significantly high (p<0.05) as compared to group 2.

Discussion. Many therapeutic modalities of therapy have been used in treatment of viral warts, most of them take months, but many of them are destructive and might cause scarring. Also, the recurrence rate after these modalities of therapy may be high. The current treatment for warts involves physical destruction of the infected cells leading to many cosmetics sequelae.[1,2] Cell mediated immunity appears to be the principle mechanism for the rejection of warts. Warts can disappear when the immune response is stimulated, in contrast, in persistent disorders of cell-mediated immunity, the prevalence, severity of warts, and the incidence of HPV related malignancy are increased.[1] The BCG has been shown to stimulate macrophages, T and B-lymphocytes, and natural killer cell function, and augment interlukin-1 production.[9] Under some circumstances, specific activation of cell mediated immunity by T cell mitogen (BCG vaccine) and exposure to cytokines, particularly interferon gamma may lead to enhanced non specific ability of activated macrophage to deal with other unrelated antigens like papilloma virus antigens.[9] In the present work, BCG vaccination had been used as a therapeutic weapon and the result showed that a full response in 39.7%, which was significantly high when compared with a response of 13.7% after placebo treatment (p-value=0.00043). Patients with viral warts who did not respond to placebo distilled water were treated with BCG vaccine and had full recovery in 42.7% which was comparable to the recovery in the first group who initially treated by BCG vaccination. The resolving rates with other modes of treatments are as follow: oral zinc sulphate 89%,[10] intralesional zinc sulphate 98% 2 weeks after the third injection.[11] Intralesional injection of interferon eradicates 40-60% of warts,[1] while single daily use for 3 months of topical salicylic acid had a clearance rate of 67% for hand warts.[2] Preparation of 20% of glutaraldehyde in aqueous solution produced a 72% cure rate.[12] The efficacy of podophyllin approaches 60% for typical genital warts,[13] and imiquimod cream when applied to anogenital warts overnight 3 times each week for 16 weeks showed a healing rate of 65%.[14]

In the present study, we noticed signs that accompanies the regression of viral warts, such as itching in all patients (100%), which was the earliest symptom, was usually mild and persisted until complete clearance of the lesions, increased size of the lesions in 80%, and some lesions become tender (30%). When there is spontaneous regression of common warts, these signs and symptoms are absent, however, they usually precede the spontaneous regression of plane warts.[2] These signs of regression are helpful in reassurance of these patients and encourage them to continue their course of treatment. According to our long clinical experience in this field and as the present work has shown, there is no actual limitation present and all patients had welcomed this new mode of therapy, and no side effects were observed apart from the scar that might be left after vaccination.

In conclusion, BCG immunotherapy of viral warts is an effective encouraging mode of therapy. Further studies are needed for further evaluation and confirmation of these present observations.

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