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# BCG In the treatment of recurrent. Genital condyloma accuminatum

## *BCG no tratamento de condiloma acuminado genital recidivante*

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**ABSTRACT:** *Introduction*: The Human Papilloma Virus (HPV) is the most prevalent sexually transmissible disease. The treatment of Condyloma Accuminatum is a great challenge because of the high recurrence rate and of the lack of any drug efficient in its elimination. *Objective*: To assess the efficacy of the treatment with Imuno BCG (Bacillus Calmette-Guérin) for bearers of condylomas recurrent for more than 2 years. *Patients and Methods*: Patients with age between 18 and 60 years, having a history of more than 2 years of genital warts, were included, attended as from 01-08-2011; bearers of serious diseases, immunodeficiency or users of immune-suppressors, being excluded. The procedure adopted began with a biopsy of the wart(s) with local anesthetic, followed by the electro-coagulation of all the warts and bases of the biopsies, a solution with 80 mg of Imuno BCG dissolved in 2 ml of saline solution 0.9% was applied to all the genital area, including the cauterized areas. The area was covered with plastic for 2 hours and afterwards washed with water. The local application of Imuno BCG was repeated for 8 consecutive weeks. At the end of the second month the cases were re-assessed. When there was clinical recurrence a new procedure with the same drug was undertaken, but with 3 weekly applications made by the patient himself for 8 weeks. *Result*: Sixteen patients completed 2-year follow-up. The cure rate was of 62.5%. Of the 10 patients cured, 6 (37.5%) used one series of Imuno BCG, 1 (6.25%) used 2 series, and 3 (18.75%) used 3 series. Of the 6 patients who were not cured, there was a reduction in the number of cauterizations from 5.5 times (over an average period of the disease of 51.6 months) to 2.4 cauterizations (over an average follow-up period of 52.3 months) after the use Imuno BCG. The collateral effects of the use of Imuno BCG were insignificant. *Conclusion*: Topical BCG is a good option for the treatment of recurrent condylomas, with minimal collateral effect. It may be used even on PPD-negative patients. However, this result must be confirmed with larger sample populations and control-group studies.

**Keywords**: Condylomata acuminata; Papillomaviridae; Mycobacterium bovis.

**RESUMO**: *Introdução***:** O Papiloma Virus Humano é a doença sexualmente transmissível de maior prevalência. O tratamento do Condiloma Acuminado é um grande desafio devido ao elevado índice de recidiva (30-70%) e à inexistência de medicamento eficaz para sua eliminação. *Objetivo***:** Avaliar a eficácia do tratamento com OncoBCG para portadores de condilomas recidivantes por mais de 2 anos. *Pacientes e métodos:* Foram incluídos **p**acientes entre 18 e 60 anos, com história de verrugas genitais há mais de 2 anos, atendidos a partir de 01-08-2011, sendo excluídos os portadores de doenças graves, imunodeficiência ou em uso de imunossupressor. O método foi: iniciar com biopsia(s) da verruga(s) com anestesia local, seguida de eletrocoagulação de todas as verrugas e bases das biopsias, e aplicação de solução com 80 mg de Onco BCG dissolvido em 2 ml de solução salina a 0,9%, em toda área genital, inclusive nas áreas cauterizadas. Cobrir a área com plástico por 2 horas, e, depois lavar com água. As aplicações locais de Onco BCG foram repetidas por 8 semanas consecutivas. No final do segundo mês os casos foram reavaliados. Quando havia recidiva clínica um novo procedimento com o mesmo medicamento era feito, porém com 3 aplicações semanais pelo próprio paciente por 8 semanas. *Resultado*: Dezesseis pacientes completaram seguimento de 2 anos. O índice de cura foi de 68,75%. Dos 11 pacientes curados, 6 (37,5%) usaram uma série de Onco BCG, dois usaram 2 (12,5%) séries, e 3 (18,75%) usaram 3 séries. Dos 5 pacientes não curados, houve redução de número de cauterizações de 5,5 vezes num período médio de doença de 51,6 meses, para 2,4 vezes de cauterizações, num período médio de acompanhamento de 52,3 meses, após uso de Onco BCG. Os efeitos colaterais com o uso do BCG são insignificantes. *Conclusão***:** BCG tópico é boa opção no tratamento para condilomas resistentes, com mínimo efeito colateral e pode ser usado mesmo nos pacientes PPD negativos. No entanto, esse resultado deve ser confirmado com maior casuística e estudo com grupo controle.

**Descritores**: Condiloma acuminado; Papillomaviridae; Mycobacterium bovis.

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## INTRODUCTION

Anogenital Human Papilloma Virus (HPV) is the most frequent sexually transmitted disease (STD) at the present time, with a prevalence of 30 to 50% in the female university students of the United States[1]. It is calculated that 75-80% of the sexually active population will be affected by HPV at some time during their lives[2]. It is important to point out that the use of preservatives diminishes the rate of contamination but does not hinder the infection[3]

The basic treatment consists of the destruction of condylomatous lesions by mechanical, physical or chemical means. All the forms of treatment, when well prescribed and adequately applied produce good results and have similar efficacy[4]. The rates of recurrence vary from 30-70%[5-7], and have significant psychological impact on both the patient and their family members. With a view to reducing the recurrence rate, many agents have been used as stimulators of local immunity[6,8].

The Imuno BCG (Bacillus Calmette-Guérin) used to reduce the recurrence of vesical tumors is constituted of inactivated Bovine Mycobacterium and acts as a stimulator of local cytotoxic immunity. It was used as a topical genital cream on bearers of HPV and shows a reduction in the recurrence of condylomas, with minimal collateral effects[9,10].

Our objective was to undertake a prospective study to assess the index of condyloma recurrence after treatment with Imuno BCG in patients who were bearers of HPV whether treated or not with other medicines, for at least two years.

### Patients and methods

Included in the study were masculine patients of between 18 and 60 years of age, with a history of genital warts of over two years and with the signed declaration of informed consent, attended in the Outpatients Department of the STD of the Urology Division of the Hospital das Clínicas, of the Medical School of the University of São Paulo (HC-FMUSP), as from 01-08-2011. Only those who had been treated and had been followed up for at least two years were included in the analysis. Bearers of serious diseases, who were immune-deficient or who were using an immune-suppressor were excluded. This study received the approval of the Ethics Commission of the HC-FMUSP.

Hemogram, glycemia, creatinin, sorology for hepatites B and C, HIV, syphilis, initial urine jet for urinary sediment, radiography of the thorax from the front position and right side and PPD were collected. The visual physical exam was made with the help of a magnifying glass with magnification of 3 and 6 times to identify papules and warts. Under local anesthetic with lidocaine 2% at the base of the places affected. One proceeded to the biopsy of the papules and/or warts followed by the electro-cauterization of the papules, warts and bases of the biopsies. The products of the biopsies were sent for pathological anatomy.

Immediately after the cauterizations 80 mg of Imuno BCG dissolved in 2 ml of saline solution at 0.9% was applied throughout the genital area, the supra-pubic region and the crural regions, including the cauterized areas. The area applied was covered with plastic of the "Magipac" type for 2 hours, followed by washing with water. The local applications of Imuno BCG were repeated once a week for 8 consecutive weeks, undertaken by the nursing staff in the Urology Outpatients Department of the HC-FMUSP.

The patients were re-examined at the end of the second month for an assessment of the results and the collateral effects. The cases who presented clinical recurrence were submitted to a new procedure and were treated again, with the same medicine, though with applications 3x per week for 8 weeks, made by the patients themselves at home. The patients who presented a new clinical recurrence were submitted to the new procedure and were treated again, with the same medicine but with applications 3x per week for 12 weeks.

The following were assessed: a) Rate of cure; b) complications: pain, local hyperemia, local and systemic wounds and infections.

## RESULT

Sixteen patients fulfilled the requirements and were included in the study. The average age of the patients was 32 (21-46) years, with a first sexual relationship at 15.3 (11-19) years of age. Each patient had intercourse, on average, with more than 21 persons (3-80) before the time of their first consultation at our service. Nine of these patients had new partners after the treatment with BCG. Before this study, three patients had never been treated and 13 of them had been treated with cauterizations and had used 5-fluorouracil or imiquimod or podophyllotoxin or podophyllin or acid. Two patients with a prepucial ring and condyloma in the prepuce were submitted to postectomy.

The patients who went for 2 years without exophytic lesions were considered cured. Of the 16 patients treated, 10 (62.50%) were free of exophytic lesions. Of the 10 patients were free of exophytic lesions, 6 (37.5%) used only one course of Imuno BCG, one (6.25%) used two series of BCG, and 3 (18.75%) used 3 series of BCG. Of the 8 patients who used a second series of Imuno BCG, 1 became free of exophytic lesions. Of the 4 patients who used a third series of Imuno BCG, 3 became free of exophytic lesions. Of the 6 patients who were free of exophytic lesions with one series of Imuno BCG, 2 were submitted to a simple cauterization. The patient who was cured with two series of Imuno BCG, was also submitted to a simple cauterization.

As regards the 6 (37.5%) patients who were not cured, there was a reduction in the number of cauterizations

from 5.5 times (without counting the use of podophyllin for 2 years and the use of acid on two other patients for the purpose of "cauterizing" the wart), with an average duration of the disease from 51.6 (24-96) months, to 2.4 cauterizations during an average period of follow-up of 52.3 (28-65) months after the use of Imuno BCG. One of these patients was classified as "not cured", but has been 17 months without exophytic lesions.

All the patients had normal blood tests and simple radiography of the thorax. Of the PPD tests before the procedures with Imuno BCG: ten had no reaction to PPD (0 mm), 5 had respective reactions of 8 mm, 10 mm, 12 mm, 17mm, 20 mm, and 1 patient did not return for the reading. The patients who had reactions to the PPD 10 mm or greater were recommended for assessment by an Infectologist, but no evidence of infection by tuberculosis was found in any of them. After the procedure with Imuno BCG, of the 10 with PPD zero mm, five remained with PPD 0 mm, one with 4 mm, two with 5 mm, one with 18 mmand one did not do PPD after Imuno BCG.

Of the patients with PPD zero prior to the Imuno BCG, 4 were submitted to the application of Imuno BCG with multiple punctures with an insulin needle in the area applied, mainly around the site of the cauterized warts. Of these 4 patients, one continued to have PPD test zero, one of 4 mm, one of 17 mm and one of 18 mm. Of these 4 patients, 2 were free of exophytic lesions. All of the patients had granulomas, which regressed spontaneously without bothering the patient. In the patient who had the PPD of 18 mm, 2 proceedings with Imuno BCG with puncture were performed, and after the second puncture, granulomas of up to 1 cm were formed. Fifteen months later, excision of the granuloma of 6 mm on the prepuce was undertaken as was cauterization of the warts. The anatomical-pathological (AP) exam of the granuloma showed granuloma with caseous necrosis with BAAR (acid-alcohol resistant bacillus) research and immune-histochemistry for Koch Bacillus negative. The AP examination of the warts was Squamous Papilloma.

Six patients with PPD test of 0 mm received BCG without puncture and five of them were cured. Of those cured who had PPD 0 mm, 3 continued to have PPD 0 mm and 2 had a reaction of 5 mm to the PPD. No patient presented local irritation, systemic reaction or fever, except for the formation of granuloma in those patients in whom a puncture had been made.

## DISCUSSION

The treatment of recurrent acuminated condylomas continues to be a challenge for medicine. Ho[11] reports that 91% of persons eliminate HPV infection in up to 2 years. Ten percent of people do not succeed in eliminating the virus and about 1% of patients present recurrent genital warts. For the purpose of reducing the rate of recurrence Bohler[12] in 1995 used BCG cream for the first time, achieving remission in 4 of his 6 patients, though they were patients with duration of the disease of less than 18months, and only one patient had had the disease for more than 2 years. We included in this present study only patients with a history of condyloma of more than two years precisely to reduce the influence of the development of the natural immunity of the body in the face of infection by HPV[11,13], in the rate of cure.

Metawea et al.[9] and Salem et al.[14] only applied BCG in patients with PPD (+). In our study we applied BCG in both PPD (+) and (-) patients, and no patient had fever or any sign of local or systemic infection. Reaction to PPD does not indicate that there will be a better result in the elimination of the warts.

BCG cream was only applied on the warts[9,10] or only to the already healed cauterized area[12]. We applied it across the whole genital, supra-pubic and crural area, whether cauterized or not, because we believe that it permits a better coverage of the medicine in those areas which are potential wart-forming ones.

Bohler[12], in the treatment of recurrent condylomas of characteristics closer to those of our patients, followed them up for more than two years in 2 cases, and followed up for up to 12 months the remaining 3 cases. Under these conditions he obtained an 83 % cure rate. Using BCG on patients who had never been treated before, Bohler et al.[10] obtained a cure rate of 60%, and Metawea et al.[9] had a cure rate of 80%, in both cases with follow-up of less than 1 year.

We counted as cured only those patients who were not recurrent after 2 years of follow-up since the last cauterization, because we had 3 patients who were recurrent at about 20 months. Our cure rate was of 62.5%, slightly inferior to Bohler's[12] in cases of recurrent condylomas; however, our inclusion criteria in terms of duration of disease and follow-up time are greater. In the 6 (37.5%) patients calculated as **un**cured, one has already gone for 17 months without warts. Two patients relapsed at close to 2 years, though they did not return for treatment.

Grupta[15] injected BCG directly into the lesions and succeeded in eliminating the wart in the two patients treated; however, our cases in which puncturing was used did not have a better result than those whose application was made only on the skin. Can it be that injection into the lesion, obtaining an effectively greater dose, has greater immunological effect?

Imiquimod cream 5%, recommended by the CDC[16], presents a wart elimination rate of 37 to 52%, with a recurrence rate of 13% at 3 months and 23% at six months' follow-up[17]. We believe that with a longer follow-up time, this recurrence rate would be comparable to ours (31.25%). Kumar et al.[18] compared intralesional BCG with imiquimod cream 5% and showed slight superior resolution in the BCG group, 67/59% ($p = 0.52$).

Bohler et al.[12] reported 1 case (16%) of fever

and edema of the penis which hindered the continuation of treatment. In another study[10] he had 2 cases (20%) of fever of 38 and 40 degrees on the first day. Metawea et al.[9] reported 5 (25%) cases of hyperemia with a passing sensation of burning. None of our patients complained of fever or hyperemia or local irritation, even in those cases in which puncturing had been used.

## CONCLUSION

Topical BCG is a good treatment option for resistant condylomas, with minimal collateral effect. It can be applied evenin patients who do not react to the PPD test. However, to obtain more affirmative conclusions greater sample populations and group control study are necessary.

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