**Efficacy of Intralesional 5-Fluorouracil versus BCG Vaccine in the Treatment of Warts**

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**ABSTRACT**

**Objective:** The aim of this work is to make a comparative study between the efficacy of intralesional BCG vaccine and intralesional combination of 5-fluorouracil (5-FU), lidocaine (L) and epinephrine (E) for the treatment of warts.

**Patients & Methods:** Sixty patients were included in the study with age range from 18 – 65 years. Patients with different types of warts (common, planter, genital, periungual warts) were selected from the outpatient clinic of Dermatology & Andrology Department of Benha University Hospital. The selected patients were randomized into two treatment groups where group (A) received intralesional 5-FU+ LE (4mL of 50 mg/mL 5-fluorouracil and 1 mL of a mixture of 20 mg/mL[2%] lidocaine and 0.0125 mg/mL epinephrine) at biweekly intervals till complete clearance of the warts. In group (B) a single wart in each patient was injected intralesionally with 0.1 ml BCG. This therapy is repeated every 3 weeks till complete clearance of the warts or for a maximum of four treatments without response.

**Results:** The number of sessions required to achieve response varied between both drugs, ranging from 1-4 sessions for BCG, and more than 6 sessions for 5-FU with time interval between sessions 2 weeks for 5-FU and 3 weeks for BCG. The study found that there was no response in 3.3% for 5-FU versus 20% for BCG. Partial response was observed in 33.3% of patients treated with 5-FU versus 40% for BCG, and 63.9% had complete response with 5-FU versus 40% for BCG. The response was better in patients who received 5-FU treatment than those who received BCG treatment regarding to the number of warts. It is also notable that the larger the number of warts the better the response. Results were higher for 5-FU in all wart types with maximum response in genital warts, while the least response was observed equally in both planter and palmer sites. It was also notable that the longer the duration of warts, the better the response to either drugs.

**Conclusion:** 5-FU was better in treating large number of warts, although BCG was easier in administration. 5-FU achieved best response in genital warts; unfortunately we were unable to compare with BCG. The second best response was in periungual warts followed by common warts. The least response was observed in plantar and palmar warts. It was also noted that larger and older warts responded better to either drugs.

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**INTRODUCTION**

Warts are benign proliferations of the skin and mucosa that are caused by infection with papillomaviruses (PVs). More than 100 Human Papilloma Virus (HPV) types have been sequenced; the actual number of genotypes is even higher

(1) HPV infection occurs through inoculation of virus into the viable epidermis through defects in the epithelium (2).

 Acquisition of HPV depends on several factors, including the location of lesions, the quantity of infectious virus...
present, the degree and nature of the contact, and the general and HPV-specific immunologic status of the exposed individual. The role of immunity and genetic susceptibility to PV infection are incompletely understood (3,4).

Most treatments for warts involve physical destruction of the infected cells as by cryotherapy using liquid nitrogen, curettage or surgically excision. Laser treatment in several different energy formats, including photodynamic therapies, can be useful for destroying warts (5,6).

5-FU is an antimetabolite that inhibits DNA and RNA synthesis, thereby preventing cell replication and proliferation. This mechanism of action may allow 5-FU to be utilized in the treatment of HPV (7).

Bacille-Calmette-Guérin (BCG) is well known for its prophylactic effects against tuberculosis. It has been also used in the treatment of malignant melanoma, transitional cell carcinoma of the bladder, in alopecia areata, in recurrent oral aphthosis and in viral warts. Its mode of action could be explained on the basis of stimulation of macrophages, natural killer cells, T and B lymphocytes that might help in the resolution of viral warts (8).

The existence of multiple treatment modalities reflects the fact that none is uniformly effective or directly antiviral. The choice of treatment depends on the location, size, number, and type of wart, as well as on the age and cooperation of the patient. Pain, inconvenience, risk of scarring, and the patient's benefits should be considered (8).

The aim of this work is to make a comparative study between the efficacy of intralesional BCG vaccine and intralesional combination of 5-fluorouracil (5-FU), lidocaine (L) and epinephrine (E) for the treatment of warts.

PATIENTS & METHODS

This study was carried out on 60 adult patients with age range from 18 – 65 years. Patients with different types of warts (common, planter, genital, periungual warts) were selected from the outpatient clinic of Dermatology & Andrology Department of Benha University Hospital. The diagnosis of warts was made by clinical examination. They were 26 males and 34 females. Exclusion criteria included patients with immunosuppression, pregnant or lactating women and patients with past history of tuberculosis.

All patients before any procedure had full history taking and signed a written informed consent which was approved by the Ethics Committee of Human Research Benha University.

The 60 patients were randomized into two treatment groups: Group A (5-FU group): received an intralesional injection of a mixture containing 4mL of 50 mg/mL 5-fluorouracil and 1 mL of a mixture of 20 mg/mL[2%] lidocaine and 0.0125 mg/mL epinephrine (8). The mixture was injected into the base of every wart using a built-in needle insulin syringe until the entire lesion begins to puff up. The actual delivered volume of solution will be adjusted according to the dimension of each lesion ranging from 0.05-0.15 cm³. Patients were injected at biweekly intervals till complete clearance of the warts or as long as there is an improvement.

Group B (BCG group): The oldest and usually the largest wart (target wart) was injected using a built in needle insulin syringe intralesionally with 0.1 ml BCG. This therapy is repeated every 3 weeks till complete clearance of the warts or for a maximum of four treatments without response (9).
Evaluation:
In both groups all patients were examined and photographed before each injection noting the number and surface area of warts. Both the treated and untreated warts were measured. During follow-up the presence or absence of response to treatment and approximate decrease in the size of warts in responding subjects were recorded. The response was evaluated as: Complete response which is defined as the complete absence of clinically apparent wart. Partial response was defined as decrease in size $> 25\%$. No response was defined as $< 25\%$ decrease in size.

RESULTS

Table (1): Comparison between the response in the 5 Fluorouracil group and the response in the BCG group in relation to number of warts

<table>
<thead>
<tr>
<th>Warts</th>
<th>Response</th>
<th>5 fluorouracil</th>
<th></th>
<th>BCG</th>
<th></th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Partial Complete Total</td>
<td>No Partial Complete Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>No 1 7 9 17</td>
<td>6 6 7 19</td>
<td></td>
<td></td>
<td></td>
<td>$0.052$</td>
</tr>
<tr>
<td></td>
<td>% 5.9 41.2 52.9 100</td>
<td>31.6 31.6 36.8 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>No - 2 1 3</td>
<td>- 4 3 7</td>
<td></td>
<td></td>
<td></td>
<td>$0.033$</td>
</tr>
<tr>
<td></td>
<td>% - 66.7 33.3 100</td>
<td>- 57.1 42.9 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>No - 1 9 10</td>
<td>- 2 2 4</td>
<td></td>
<td></td>
<td></td>
<td>$0.011$</td>
</tr>
<tr>
<td></td>
<td>% - 10.0 90.0 100</td>
<td>- 50 50 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>No 1 10 19 30</td>
<td>6 12 12 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% 3.3 33.3 63.3 100</td>
<td>20 40 40 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi square ($\chi^2$)</td>
<td>5.526</td>
<td>8.505</td>
<td>$0.003$ (highly significant)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $P >0.05$ (non-significant), $<0.05$ (significant), $<0.01$ (highly significant), $<0.001$ (very highly significant).

Table (1) compares the response in 5-FU (gr. A) and the response in BCG (gr. B) in relation to number of warts and showed that patients who had 1-5 warts in gr. A had no response in 1 pt. (5.9\%) vs. 6 pts. (31.6\%) in gr. B. Partial response was observed in 7 pts. (41.2\%) in gr A vs. 6 pts. (31.6\%) in gr. B. Complete response was observed in 9 pts. (52.9\%) in gr. A vs. 7 pts. (36.8\%) in gr. B. The statistical difference between 5FU and BCG was insignificant ($p > 0.05$) in this group. On the other hand, all patients who had 5-10 warts showed medical response which varied from partial response in 2 pts. (66.7\%) in gr. A vs. 4 pts. (57.1\%) in gr. B and complete response was observed in 1 pt. (33.3\%) in gr. A vs. 3 pts. (42.9\%) in gr. B. All patients who had $> 10$ warts responded to therapy. Partial response was detected in 1 pt. (10\%) in gr. A vs. 2 pts. (50\%) in gr. B, while complete response was observed in 9 pts. (90\%) of gr. A vs. 2 pts. (50\%) in gr. B.
Table (2): Comparison between response in 5FU group and BCG group as regard type of wart.

<table>
<thead>
<tr>
<th>Type of wart</th>
<th>5 fluorouracil</th>
<th>BCG</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>Common</td>
<td>No</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>30.0</td>
<td>70.0</td>
</tr>
<tr>
<td>Plantar</td>
<td>No</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>6.3</td>
<td>31.3</td>
</tr>
<tr>
<td>Palmer</td>
<td>No</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>-</td>
<td>37.5</td>
</tr>
<tr>
<td>Periungual</td>
<td>No</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>-</td>
<td>25.0</td>
</tr>
<tr>
<td>Total</td>
<td>No</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>3.3</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Table (2) demonstrates that the best response was in 6 periungual (75%) and 14 common warts (70%) in gr. A vs. 7 (35%) and 2 (33.3%) simultaneously in gr. B with statistically insignificant difference between both groups (p value > 0.05). 5-FU showed marvelous effects on 4 genital warts (100%), but no cases were included in the BCG group.

Table (3): Comparison between the response in the 5 Fluorouracil group and the response in the BCG group in relation to size of warts

<table>
<thead>
<tr>
<th>Size</th>
<th>5 fluorouracil</th>
<th>BCG</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Partial</td>
<td>Complete</td>
</tr>
<tr>
<td>&lt;0.5 cm</td>
<td>N</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>7.1</td>
<td>21.4</td>
</tr>
<tr>
<td>0.5-1cm</td>
<td>N</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>5.0</td>
<td>35.0</td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>N</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>8.0</td>
<td>92.0</td>
</tr>
<tr>
<td>Total</td>
<td>N</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>5.2</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Table (3) reveals incomparable response accomplished in 11 warts (92%) > 1cm in gr. A vs. 8 warts (66.6%) in gr. B. The second highest response was in 19 warts (71.4%) < 0.5cm followed by 12 warts (60%) > 0.5-1cm in gr. A. This was reversed in gr. B where 10 warts (43.4%) of 0.5-1cm showed better response than 5 warts (29.4%) <0.5cm.

The relation between the three sizes of warts in relation to their therapeutic response revealed statistically significant difference (p < 0.05) between both groups.
Comparing between 5-FU and BCG response to treatment as regard to duration of warts

Chart (1) displays the impact of duration of wart lesions on the response to therapy. Complete response was gained by 19 pts. (63.3%) treated with 5-FU whom their lesions were more than 23 months vs. 12 pts. (40%) treated with BCG with lesions dating 19 months. Comparable results were seen in lesions with 10 months duration in both groups. No response was seen in 3.3% cases of 5-FU with lesions duration 6 months versus 20% for BCG with lesions duration 8 months. The difference regarding the duration of the lesions and response was statistically significant ($p < 0.05$).

**DISCUSSION**

Patients and clinicians experience the frustration of treatment results of cutaneous viral warts caused by infection with the human papilloma virus (HPV) \(^{(10)}\). Although seemingly harmless, warts cause quite a lot of morbidity. They can greatly affect the patients’ quality of life by causing social embarrassment because they are cosmetically unacceptable to society in addition to persistence and/or recurrence \(^{(11)}\).

The aim of this study was to evaluate and compare between the efficacy of intralesolesial combination of 5 fluorouracil, epinephrine and lidocaine, versus intralesolesial BCG Vaccine. To our knowledge there is no published papers comparing the efficacy of both methods.

Comparing the results of both groups in regard to the number of warts, our results demonstrated that the response was better in the patients who received 5-FU than BCG treatment. It is also notable that the larger the number of warts, the better the response. This could be explained by the fact that patients who had a larger number of warts, continue to follow up the injection treatment more than those with fewer warts, who may be reluctant to continue therapy, or may shift to another treatment.

This is in contrast to the reporting of Youn et al.\(^{(12)}\) who suggested that if the patient had few recent warts he was easier to manage.

Although the 5-FU results seem outstanding compared to BCG, it is worth mentioning that the greater the number of warts the more burden to the doctor and patient in 5-FU injection, while BCG has the advantage of injecting a single wart that not only clears the local wart but also distant warts as well\(^{(13)}\).

The response of different types of warts to either treatments was higher for 5-FU in all warts types with statistically insignificant difference with maximum response in genital warts (100%) [Fig. 1].
We did not compare it to BCG due to its severe side effects which would be intolerable to the patient. The second best response was observed in periungual warts 75% versus 33.3% for BCG followed by common warts 70% versus 38.9% for BCG [Fig. 2]. The least response was observed equally in both planter [Fig. 3] and palmer warts 62.5% in 5-FU while BCG achieved 50% and 55.5% respectively [Fig. 4]. The same result was reported by Soni et al.\(^\text{(14)}\) who reported that palmoplanter and periungual warts are particularly difficult to treat. Also, Sharquie et al.\(^\text{(8)}\) who used BCG vaccine for treatment of warts found that the response was distributed among different types of warts with 63.3% for common warts, 23.3% plane and 13.3% planter being the least to improve as our study found. Interestingly this contradicts with Youn et al.\(^\text{(12)}\) who reported that plantar warts showed a higher cure rate than the other types and believed it was due to the high effectiveness of paring (removing excessive keratin) before applying treatment. It is worth noting that in periungual warts we did not use epinephrine as it is contraindicated in this site.

We categorized the results for 5-FU and BCG according to size of warts and it was noticed that larger number and bigger size had better response. No work was cited connecting the size of the wart to the response.

This study showed that the longer the wart duration the better the response to therapy to either 5-FU or BCG. This may be attributed to the patients’ interest for treatment. Bruggink et al.\(^\text{(15)}\) stated that cure rates were lower among participants whose warts had been present for six or more months at baseline than among those whose warts had been present for a shorter duration. Immunological factors could play a role. Also, Choi et al.\(^\text{(16)}\) stated that generally speaking, numerous warts and longer treatment periods imply higher therapeutic difficulties.

The number of sessions required to achieve the above mentioned results varied between both drugs, for BCG we stopped at 4 sessions because the side effects were intolerable to the patient and no further progress was noticed. As for 5-FU, the action was direct on the wart and repeated with every injection, so we continued further to achieve more results.

By the end of the 3\(^\text{rd}\) session 71.43% of patients treated with 5-FU had complete clearance vs. 39.3% for BCG. Although this seems in favor of BCG yet by that time 21.4% in 5-FU did not show any response at all. During this period all cases had some sort of response to 5-FU. At the end of the 6\(^\text{th}\) session the percent of complete response had increased (50%) to 5-FU.

Similarly, Sharquie et al.\(^\text{(8)}\) used BCG vaccine for treatment of warts and found that 40% achieved complete response after the third session. This also comes in accordance with the findings of Youn et al.\(^\text{(12)}\) which stated that immune-associated methods evoke better cure results than local destructive methods. They suggested that these modalities were able to prevent the recurrence of viral warts by maintaining the immune response. Also, Lipke\(^\text{(17)}\) reported that viable bacillus Calmette-Guérin treatment is based on stimulation of the local immune response.

The time between the sessions in 5-FU treatment as previously done by others was one week\(^\text{(9,20)}\), but as the work progressed it was changed to every two week as this was found to be more convenient to the patient which added more to adherence to treatment regimen, after one week the wart was still inflamed and sometimes swollen which made the second injection more painful, so a time interval of two weeks allows the patient to rest, the wart to be less inflamed and sometimes slightly shrunken. Our findings contradict with Youn et al\(^\text{(12)}\) who claimed that decreasing the time intervals between sessions, in local destructive methods, yielded better response.
For BCG the time between sessions was about one month, to allow the severe local inflammatory reaction to subside and to allow time for the immune stimulation to take place before further stimulating it. This was the same time frame used by Sharquie et al.\(^8\) who treated warts with BCG vaccine with one month interval.

The overall response to either treatment modalities could be summarized as no response in 3.3% for 5-FU versus 20% for BCG. Partial response in 33.3% of patients treated with 5-FU versus 40% for BCG, and finally 63.9% complete response with 5FU versus 40% for BCG. The complete response obtained by 5-FU was almost similar to that reported by Sri et al.\(^8\) who mentioned that 5-Fluorouracil has been used both topically and intrallesionally in the treatment of warts, with clearance rates up to 70%.

A similar study was conducted by Sharquie et al.\(^8\) who tested BCG vaccine in treatment of various types of warts and achieved overall response 40% also. Yazdanfar et al.\(^9\) reported complete response in 64.7% of the warts treated with 5-FU. Partial response was seen in 17.6% of the common warts treated with 5-FU. Iscimen et al.\(^19\) obtained clearance rates of 88% (70% complete response and 18% partial response). Although their results are close to ours yet, his search was limited to common warts and did not include any other type. Swinehart et al.\(^20\) treated individual anogenital lesions with 5-FU once weekly for up to six weeks. They reported clearance rates ranging from 77%. Our results were superior in this type where 100% showed complete response.

In our study we noticed that the intensity of pain varied greatly from one patient to another and from one site of injection to another. Hyperpigmentation occurred in 20% of cases, in the sun exposed areas due to leakage which may occurs during injection. Necrosis occurred in 20% of cases which we believe it was a therapeutic effect rather than a side effect, as wart which showed necrosis usually resolves by the following session. Ulcers were encountered in 10% of cases due to the vasoconstrictor effect of epinephrine along with the cytotoxic effect of 5-FU, but this side effect was always accompanied by wart resolution. Lymphadenitis was seen in a single case (3.3%) and was due to 2ry infection at the site of injection.

This coincides with the work cited in literature that reported adverse reactions including local inflammation, irritation, pain, erythema, edema, skin discoloration, ulcerations and erosions. These reactions gradually subsided and none of them caused significant cosmetic sequelae\(^9,20,21\).

For BCG, the side effects were slightly different, while pain was the dominant side effect for 5-FU, it was only observed in 53.3% of BCG patients and constitutional symptoms (malaise and fever) that were absent with 5-FU were found in all cases treated with BCG. They required the use of analgesics and antipyretics, and were usually described by the patient as having a common cold. Ulceration was also an important side effect of BCG occurring in 26.7% of patients and was usually preceded by a local inflammatory reaction perceived by the patient as an abscess. Necrosis was observed in 16.7% of patients as another sequel of the local inflammatory reaction. Lymphadenitis, although uncommon, 6.7% was a troublesome side effect which necessitates treatment with antituberculous drugs for 3 months. These findings were similar to those reported by Sharquie et al.\(^8\). Finally we agree with Choi, et al.\(^16\) who stated that immunotherapy showed clear clinical benefits in the treatment of warts, and is particularly used in refractory warts which are unresponsive to other modalities.

**Conclusion:** The superiority of 5-FU was elucidated compared to BCG in the treatment of various types of warts. However, BCG was easier for administration.
**Figure (1a)** genital warts before treatment with 5-FU

**Figure (1b):** Genital warts after treatment with 5-FU

**Figure (2a):** Periungual warts before treatment with 5-FU

**Figure (2b):** Periungual warts after treatment with 5-FU

**Figure (3a):** Planter warts before treatment with 5-FU

**Figure (3b):** Planter warts after treatment with 5-FU

**Figure (4a):** Palmer wart before treatment with BCG

**Figure (4b):** Palmer wart before treatment with BCG
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