

# The Comparison Between Topical 5-Fluorouracil and Trichloroacetic Acid in The Treatment of External Genital Condyloma Accuminatum

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**OBJECTIVE:** To investigate the effects of fluorouracil cream and 80% trichloroacetic acid solution in the treatment of condyloma accuminatum.

**STUDY DESIGN:** 35 non-pregnant women with a diagnosis of vulvar condyloma accuminatum were randomly assigned to two groups as,5-fluorouracil group (n=17) and trichloroacetic acid group (n=18). All patients were examined after 7 days and after 6 months and were evaluated with respect to the effectiveness, side effects and recurrence rates.

**RESULTS AND CONCLUSION :** Both methods were found to be effective in the treatment of external condyloma accuminatum. When the two groups were evaluated with respect to cost per patient, the average cost was detected to be 2 USD for the trichloroacetic acid group and 20 USD for the 5-fluorouracil group.

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**Key Words:** 5-fluorouracil, Trichloroacetic acid, Condyloma accuminatum

Human papilloma virus (HPV) is a DNA virus which belongs to the papovaviridae family. These viruses are located at moist genital regions and are usually transmitted sexually. They cause characteristic proliferation on epidermal and mucosal surfaces. The role of HPV in genital infections is increasingly growing. It is the third most common factor of sexually transmitted diseases after gonorrhoeae and Chlamydia and the most common one among sexually transmitted viruses

Condyloma accuminatum results from the infection of the lower genital system by the Human papilloma virus. Papillary protuberances are initially small and over time; they combine and form large cauliflower-like masses. The cells of the whole system should be expected to be infected, from the cervix to the vulva and the perianal skin. After the identification of specific types of HPV, these viruses have been determined to be the major factors in the development of CIN, VIN and cervical cancer.<sup>1</sup>

This study was performed to compare the effectiveness, costs, side effects and recurrence rates of topical 5-FU cream and 80% trichloroacetic acid solution, used for the treatment of condyloma accuminatum.

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## Material and Method

This study is approved by Haydarpaşa Numune Training and Research Hospital's Educational and Planning Committee.

After consent was obtained from the educational planning and coordination board of our hospital, 35 non-pregnant women, between 17 and 46 years of age, who consulted Haydarpaşa Numune Hospital, Polyclinic of Gynecology and Obstetrics for vulvar condyloma were included in the study. The patients were randomly assigned to two groups as, 5-fluorouracil (5-FU) group (n=17) and trichloroacetic acid (TCA) group (n=18). The demographic parameters of the patients in both groups were evaluated, including the age, gravida, parity, abortion, curettage, number of children (Table 1). Pregnant women and patients with a history of cancer, diabetes mellitus, immunosuppressive disease, and immunosuppressive treatment were excluded from the study. Cervical smears were obtained from all the patients and the smear results were evaluated by the Papanicolaou test. All patients underwent cervical, vaginal and vulvar colposcopic examinations prior to treatment. The lesions were observed to be multifocal in all patients. No lesion was detected on posterior or lateral vaginal walls.

Table 1. The response given to medications by the patients

Medication	Complete response	Partial response	No response	Total
%80 TCA	15	3	-	18
5 FU cream	10	5	2	17
Total	25	8	2	35

During treatment; 17 patients in the Group 5-FU were topically administered 5% cream once daily for a week. The 80%

solution to be applied for the TCA group was prepared by mixing 40 ml of trichloroacetic acid with 10 ml of 0.9% NaCl and administered locally to 18 patients twice at an interval of 4 days. All patients were asked to participate in a control examination after 7 days and after 6 months following the treatment. By inspection, the treatments administered to the patients were evaluated. The response given to treatment was assessed as complete response (the lesions disappear completely), partial response (partially improved lesions) or no response (no change detected in lesions). The treatment protocol was administered once again to patients with partial response and those with no response and they were controlled one week later. The patients who gave partial response or no response to the drugs after the additional treatment were referred to cryotherapy. The side effects of the drugs were investigated (erythema, sensation of burning, pruritus). The drugs were also evaluated with respect to cost. The treated patients underwent a control examination after 6 months and evaluated with respect to recurrence. The presence of a difference in recurrence between the two groups was investigated.

For the statistical analysis, all data were recorded on the excel data base. This data base was transferred to the SPSS (statistical package for social sciences) data base for the statistical analysis. Student t test was used for the two independent groups for the comparison of the inter-group homogenization of the demographic parameters. For the comparison of data expressed in ratio, including the percentages of within-group responses to treatment, rates of side effects and rates of requirement for additional treatment, Pearson's chi-square test or Fischer's exact test was used. The alpha significance level was accepted as 0.05 ( $p < 0.05$ ) for type 1 errors.

## Result

When the two groups treated with 80% TCA and 5-FU were compared with respect to demographic parameters, no statistical inter-group difference was detected .

In both groups, the response given to treatment was assessed as complete, partial or no response. The distribution of responses is presented in Table 1 .

When these responses were compared by the chi-square test, the value found for the expected cells is less than 5 (the minimum expected value 0.97), therefore the patients with partial or no response to treatment by the chi-square test were collected in a group versus patients with complete response to treatment. By conversion to a four-cell table, a minimum expected value of 4.86 was achieved. When Fischer's exact test was applied, non-parametric test result was detected as  $p=0.146$  and by the Pearson's chi-square test, the parametric test result was detected as  $p=0.109$ . Although the likelihood of the 80% TCA to produce a complete response was determined to be 2.62 folds, in comparison to 5-Fu cream (Likelihood

ratio=2.62,  $p= (0.105)$  and (OR(odds ratio)=3.5), this value was found to be between 0.727 and 16.848 within the 95% confidence interval, and this value was not determined to be statistically significant.

3 patients in the 80% TCA group and 7 patients in the 5-FU group required additional treatment and thus, received additional treatment (Table 2). When the two groups were compared by Fisher's exact test with respect to requirement for additional treatment, no significant inter-group difference was detected ( $p=0.146$ ).

Table 2. Data of requirement for additional treatment

	No additional treatment	Additional treatment administered	Total
80% TCA	15	3	18
5 FU cream	10	7	17
Total	25	10	35

A total of 10 patients in both groups with complete, partial and no response to additional treatment were analyzed (Table 3), no significant difference was detected between the groups with respect to response to additional treatment ( $p=0.574$ ).

Table 3. Response to additional treatment

	Complete response	Partial response	No response	Total
%80 TCA	2	1	0	3
5 FU cream	3	2	2	7
Total	5	3	2	10

The medications used in the two groups were compared with respect to side effects and no statistically significant difference was detected. When the side effects were compared among themselves, the sensation of burning was observed to be significantly more in the TCA group than in the 5-FU group

A total of 28 patients participated in the control examination performed 6 months later for the evaluation of recurrence. Recurrence was detected in 6 patients in the TCA group and 1 patient in the 5-FU group. When the treatments were compared, the difference was not found to be statistically significant (OR 95%) (Table 4).

Table 4. Recurrence results

	No recurrence	Recurrence observed	Not participated in the control examination	Total
80%TCA	9	6	3	18
5 FU cream	12	1	4	17
Total	21	7	7	35
%	60	20	20	100

The smear results of the 35 patients included in our study

were evaluated and 34 patients were determined to be class I and one patient was determined to be class II (ASCUS). Colposcopy was performed in the patient with the smear result of ASCUS and interpreted as normal.

Costs were calculated per patient and found to be 2 USD for the TCA solution and 20 USD for the 5-FU cream in average.

## Conclusion

Genital condylomas are one of the leading sexually transmitted diseases and they are known to be caused by HPV. After the identification of specific types of HPV, these viruses have been determined to be one of the major factors in the development of CIN, VIN and cervical cancer. The inability to provide a complete eradication leads to significant clinical problems and recurrences are observed frequently.

In a study performed by Krebs<sup>2</sup> in 49 non-pregnant women with vulvar condylomas who received topical 5-FU every night for 6 weeks and subsequently, once weekly for 10 weeks, 71% of the patients were reported to give a response (41% complete, 30% partial) and 29% of the patients were reported to give no response to treatment. The study also reported that periodic administration could be preferred more than continuous treatment. In a study by Abdullah et. al.<sup>3</sup> involving 86 patients with external genital condylomas, TCA treatment and cryotherapy were compared, and cryotherapy was reported to be more effective than TCA treatment in patients with external genital condylomas. In another study performed by Pride et.al.<sup>4</sup> in 19 female patients with external condylomas, who received topical 5-FU for 7 days, 68.4% of the patients were reported to give a complete response and one patient was reported to give no response to treatment (5.2%).

In our study, 35 patients with external anogenital condyloma accuminatum, who consulted our clinic, were assigned to two groups by simple randomization method, and the current therapeutical approaches, treatment with 5-FU 5% cream and 80% TCA administration were compared. When the two groups were compared with respect to demographic parameters, no statistically significant difference was observed and evaluation was made between the two homogenous groups.

When the response given to the treatment modalities was evaluated, complete and partial response was detected to be achieved respectively in 83.3% and 16.7% of the patients in the TCA group whereas these ratios were detected as 58.8% and 29.5%, respectively in the 5-FU group. There was no patient who gave no response to treatment in the TCA group, while no response was achieved in 11.7% of the patients in the 5-FU group. The complete response rate for TCA is reported to be 70% in the literature, however we detected a complete response rate of 83.3% and found this difference attributable

to the fact that we used a TCA solution of 80% and administered it twice a week. In the literature, the complete response rate is reported to be between 60% and 90% for 5-FU. In our study, we detected a complete response rate of 58.8% for this group, which was in compliance with the literature.

In the study performed by Krebs<sup>6</sup> in 20 non-pregnant women with vaginal condyloma accuminatum to evaluate the efficacy of topical 5-FU administered weekly for 10 weeks, 17 patients (85%) were reported to give a complete response and 3 patients with no response were reported to give a complete response after another treatment regimen administered twice weekly. In our study, we analyzed a total of 10 patients in the both groups who gave complete, partial or no response to the additional treatment. Although the requirement for an additional treatment was lower in the TCA group, compared to the 5-FU group, the inter-group difference was not found statistically significant ( $p=0.574$ ).

In the study performed by Abdullah et al.<sup>3</sup> in patients with external genital condylomas, 30% of the patients using TCA were reported to develop ulceration. In another study performed by Beutner et al.<sup>7</sup> to compare podofilox with bichloroacetic acid or trichloroacetic acid, podofilox was reported to have certain advantages, including a lower toxicity, relatively less side effects and a low incidence of complications. In another study, less than 10% of the 5-FU administered was absorbed by the skin and relatively less side effects were observed when it was topically applied on skin.<sup>8</sup>

In our study, we evaluated the medications used in both groups with respect to their side effects and found no significant inter-group difference. When the side effects were evaluated among themselves, the sensation of burning was detected to be significantly more in the TCA group than in the 5-FU group.

In a study performed by Krebs,<sup>6</sup> among patients who were followed via cytology and colposcopy for a mean of 15.8 months, 16 patients were reported to experience no recurrence, 2 patients were reported to have recurrence and 2 patients discontinued the study. In another study performed by Krebs<sup>9</sup> involving 90 patients randomized to treatment groups, the efficacy of 5-FU in decreasing recurrence of vulvar and vaginal lesions was investigated. During the follow-up period of 9-22 months (14.4 in average), 6 patients (13%) in the group receiving 5-FU prophylaxis and 17 patients (38%) in the group receiving no treatment were reported to have recurrences. This difference in recurrence between the group receiving prophylactic treatment and the group with no prophylactic treatment was reported to be significant and maintenance treatment with 5-FU was detected to be more effective in patients with multiple lesions, multiple organ involvement and immunodeficiency. In the clinical trials performed, the

recurrence rate was reported to be 38% for 80% TCA, whereas this rate was reported to be 10% for 5-FU.<sup>5</sup>

A total of 28 patients participated in the control examination performed 6 months later to evaluate the treatment outcomes and the recurrence. In our study, 60% of all the patients had no recurrence, while 20% had, and 20% of the patients didn't participate in the control examination. 6 patients in the TCA group (40%) and one patient (7.6%) in the 5-FU group were detected to have recurrences. The inter-group difference was not found statistically significant. The recurrences observed in both groups were found to comply with the literature.

The smear results of 35 patients who participated in our study were evaluated and one patient (2.85%) was determined to be of Class II (ASCUS). In the literature, the ASCUS rate is reported to be between 3 – 5%, when the standard diagnostic criteria are used.<sup>10</sup> In our study, we detected no increase in pathological cervical smear results for patients with external condyloma accuminatum.

When the groups were compared with respect to cost per patient, the cost was determined to be 2 \$ and 20 \$ respectively for the TCA and 5-FU group.

Both treatment methods were found to be effective in the treatment of external condyloma accuminatum. Although no statistically significant difference was detected between the two groups with respect to recurrence and side effects, relatively less recurrences and side effects were observed in the group receiving treatment with 5-FU (1 recurrence, 3 cases of erythema, 1 case of burning sensation), compared to the TCA group (6 recurrences, 14 cases of burning sensation, 2 cases of pruritus). When the groups were evaluated with respect to cost per patient, the average cost was determined to be 2 \$ and 20

\$ respectively for the 80%TCA and 5-FU group.

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