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The Efficacy of Podophyllin Cautery Added to Surgical Excision for Eradication of Vulvar Condylomata Accuminata; Randomized Controlled Trial

Hussein O. Soliman[1*], Yossra Lashin[2]

[1]Department of Surgical Oncology, National Cancer Institute, Cairo University, Giza, Egypt
[2]Department of Gynecology and Obstetrics, Faculty of Medicine, Cairo University, Giza, Egypt
Email: *soliman@daad-alumni.de

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Abstract

Context: Condyloma acuminatum is a common morbidity caused by human papillomavirus infection. **Objective:** To compare the recurrence rate after surgical excision with or without podophyllin cautery. **Design, Setting, Participants:** Sixty women were enrolled in a study that was conducted in Cairo from Jan-2017 to Mar-2018. **Interventions:** All women received the same preparations. After randomization; in the study group (N = 30), podophyllin cautery was added to surgical removal in the follow-up period. In the control group (N = 30), only surgical removal was used. **Main Outcome Measure:** The main outcome measure was the estimation of the recurrence of the lesion during the follow-up period. The secondary outcome measures were the incidence of adverse events. **Results:** Both groups were comparable (p-value > 0.05) with regard to the age and BMI. Recurrence was significantly lower (P = 0.001) in the study group than the control group. In the study group, five cases (17.2%) have recurrence whereas, in the control group, 18 (60.0%) had suffered recurrence. The ARR was 42.8% (CI 95%: 18% - 60.9%) with RR of 0.29 (CI 95%: 0.12% - 0.67%) and NNT2 (CI 95%: 6% - 2%). During the follow-up period, 19 cases (65.5%) of the study group experienced pain versus only eight cases (26.7%) in the control group (p = 0.003). However, the development of scars was less in the study group 7 (24.1%) than in the control group 19 (63.3%), (p = 0.002). **Conclusion:** Podophyllin cautery, when added to surgical removal, is effective in decreasing the incidence recurrence in cases with condylomata acuminata.

Keywords

Condyloma Acuminatum, Recurrence, Adverse Events, Podophyllin Cautery,

Surgical Excision

1. Introduction

The anogenital wart, condyloma acuminatum (CA) is caused by human papillomavirus (HPV) infection. Symptomatic genital warts are seen in at least 1% of the age group of 15 - 49 years [1] [2] with about 50% or less being infected with HPV at some point in their lifetime [3].

Genital warts have psychological and physical impacts on patients. Despite that warts are often asymptomatic; at sometimes they can cause itching, burning, pain, irritation, or bleeding especially during sexual activity [3].

According to the 2012 European guideline for the management of anogenital warts, the treatment for CA range from self-application of topical agents like podophyllotoxin (0.15% cream or 0.5% solution) and imiquimod (5% cream) to clinic-based therapies like cryotherapy, trichloroacetic acid, electrosurgery, scissors excision, curettage or laser therapy. Formal surgery is reserved for large warts. There is no evidence that one type of therapy is significantly superior to another one or even appropriate for all types of warts. The data confirms that only surgical therapies have primary clearance rate approaching 100% and that recurrence occurs after all treatments with a rate of 20% - 30% or more. All therapies are associated with local skin reactions including itching, burning, erosions, and pain [4].

To the best of our knowledge, there is only one published research study that studied the effect of adding podophyllin cautery to surgical excision for the eradication of vulvar CA. Thus, the rationale which intended for this parallel randomized controlled study was to test the hypothesis that adding podophyllin cautery to surgical excision will decrease the recurrence rate of CA more than surgical removal only.

2. Materials and Methods

2.1. Study Design

This controlled, randomized, and parallel trial was conducted in Cairo University Hospital and two private centers, Cairo, Egypt during the period January 2017 to March 2018. The study conformed to the Declaration of Helsinki principles and following the Medical Research Involving Human Subjects Act. The Bio-Medical Research Ethics Committee approved it at Cairo University. The purpose of the study was explained in simple and lay Arabic language to all women before their enrollment to the study, and an informed consent form was signed by and obtained from all those enrolled.

Women meeting all of the following criteria were considered for enrollment: aged 20 - 40 years, normal BMI, sexually active, married with vulvar condylomata accuminata coming to the centers during the period of the study.

Women presenting with any of the following were excluded from the study: previous history of infection with HPV, current history of other sexually transmitted diseases or pregnancy.

2.2. Randomization and Blinding

Before the trial, computer-generated randomization schedules were generated and placed in sequentially numbered sealed opaque envelopes.

Block randomization with a block size of 4was used with 1:1 ratio of both groups (study and control groups). Recruitment was made before revealing the allocation. Sealed opaque envelope method was used for the allocation. The allocation was blind to both recruiter and participant.

2.3. Interventions in Both Groups

The two groups were subjected to the same preparation. For all women in both the study and the control groups, surgical excision of the wart with scalpel was made. During the follow-up period (12 weeks) podophyllin cautery with podophyllin 0.5% solutionwas made once per week only for the study group only (30 women). All women were followed up every week for the entire follow-up period.

2.4. Procedures

All women were subjected to detailed history (gyencologic, medical, and surgical), complete general examination to exclude the presence of any disorders. Gynecologic examinations were made systematically according to the centre's protocol.

All surgeries were done under local anaesthesia. All women were followed up postoperatively for 24-hours then dismissed.

2.5. Outcome Measures

The primary outcome measure was the incidence of recurrence of the lesion in both groups during the follow-up period. The secondary outcome measure was the incidence of side effects the follow-up period.

2.6. Statistical Analysis

Sample size calculation suggested that a minimum of 28 subjects per group is required to detect 12% difference in incidence of postoperative bleeding between groups with a standard deviation of 1.56% (taking type I or α error of 5%, type II or β error of 20%). The 12% difference was based on a pilot study on 20 participants, 10 in each group. We decided to include 30 patients per group to allow for dropouts.

All statistical analyses were made by the intention to treat analysis method. All statistical tests were made using a significance level of 95%. P-value < 0.05 was considered statistically significant. SPSS software (version 20.0, SSPS Inc., Chi-

cago, IL, USA) was used for the statistical analyses. Data were presented as (mean ± SD) for continuous variables and as frequency and percent for categorical variables. Comparisons between groups were made using Chi-square test for categorical variable and the independent t-test for the continuous variables. For the analysis of the primary outcome variable, we calculated the relative risk (RR) with 95% confidence interval, the absolute risk reduction (ARR), the relative risk reduction (RRR) and the number needed to treat (NNT).

3. Results

Ninety-five (95) women with CA who came to the centers were asked to participate in the study. Eight women declined to participate, and 27 women did not meet the inclusion criteria (10 due to pregnancy and 17 were out of the age range), leaving 60 eligible for randomization with 30assigned to each group. One woman lost follow up and excluded from the per-protocol analysis. The dispositions of these women are shown in Figure 1.

3.1. Baseline Characteristics

Both the study and the control groups were comparable with regard their baseline characteristics. There was no statistically significant difference ($p > 0.05$) between the two groups regarding the age and BMI, as shown in Table 1.

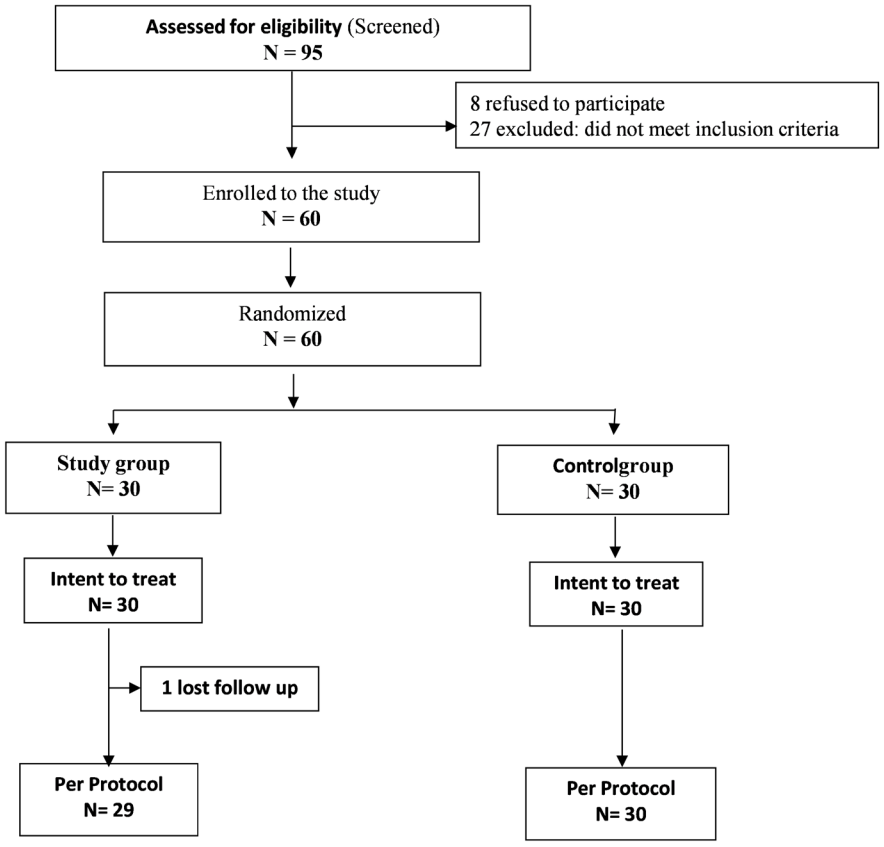

Figure 1. Consort diagram.

Table 1. Patients' characteristics.

	Study group N = 30	Control group N = 30	p-value
Age in years	29.60 (6.17)	29.60 (6.17)	0.976
BMI (kg/m^2)	22.00 (1.37)	21.62 (1.36)	0.289

3.2. Study Outcomes

During the follow-up period, 19 cases (65.5%) of the study group experienced pain versus only eight cases (26.7%) in the control group (p = 0.003). However, the development of scars was less in the study group 7 (24.1%) than in the control group 19 (63.3%), (p = 0.002).

Recurrence of the lesion was significantly lower (p = 0.001) in the study group than the control group. In the study group, five cases (17.2%) have recurrence whereas, in the control group, 18 (60.0%) had suffered recurrence. The ARR was 42.8% (CI 95%: 18% - 60.9%) with RR of 0.29% (CI 95%: 0.12% - 0.67%) and number needed to treat (NNT) 2% (CI 95%: 6% - 2%), as shown in **Table 2**.

4. Discussion

Because of the high rate of recurrence of CA after any modality of treatment (20% - 30% or more) [4], researchers have to seek for more methods or combination of methods to reduce this high rate. This randomized controlled study was conducted to test the hypothesis that adding podophyllin cautery to surgical excision will decrease the recurrence rate of CA more than surgical removal only in cases with CA.

It was quite evident from this study that adding podophyllin cautery to surgical excision will further reduce the recurrence rate of CA where the ARR was 42.8% (CI 95%: 18% - 60.9%) with RR of 0.29% (CI 95%: 0.12% - 0.67%) and NNT 2% (CI 95%: 6% - 2%). Furthermore, the development of scars was lower in the study group than in the control group. However, during the follow-up period, pain was experienced more in the study group than in the control group.

According to the results of randomized clinical trials, data suggested that podophyllin resin is more effective than placebo and that, surgical treatments are largely equivalent [5].

The antimitotic agent, podophyllin resin, one of the oldest nonsurgical treatments available for CA, destroys warts by inducing tissue necrosis locally. It is used compounded as a 10% - 25% suspension in tincture benzoin [6] [7].

The extensive evaluation of efficacy [5] [6] [7] and safety of podophyllin resin showed that despite its efficacy, a variety of adverse effects including suppression of bone marrow, liver cell dysfunction, neuropsychological symptoms and gastrointestinal disturbance, and acute abdominal pain have been reported [8]-[20]. The recurrence rate after using podophyllin alone has been reported to be 65% of cases [21]-[26]. Due to the availability of a large number of alternative modalities of treatment and these reports of side effects, some European

Table 2. Treatment outcome.

	Study group N = 29	Control group N = 30	p-value
Pain	19 (65.5%)	8 (26.7%)	**0.003**
Scar	7 (24.1%)	19 (63.3%)	**0.002**
Recurrence	5 (17.2%)	18 (60.0%)	**0.001**
Relative risk (RR)	0.29 (0.12 to 0.67)		
Relative risk reduction (RRR)	71% (32.8% - 87.7%)		
Absolute risk reduction (ARR)	42.8% (18% - 60.9%)		
Number needed to treat (NNT)	2 (6 - 2)		

experts recommended against its use in the primary-care settings especially in large dose over an extensive area of skin surfaces which favored systemic absorption [8]. In the current study, we used podophyllin in lower frequency to avoid the adverse events.

Surgical removal by scalpel directly removes wart-affected tissues. Clinical research studies reported that 35% - 100% of cases showed clearance of visible warts immediately with recurrence rate of 19% - 29% one year after excision [4] [27] [28]. Podophyllin alone appears to be less effective than surgical excision [27] [28] [29].

The evidence of the current study is fairly strong to prove that adding podophyllin cautery to surgical excision will decrease the recurrence rate of CA more than surgical removal only in cases with CA. Also, adding podophyllin cautery to surgical excision is safe.

5. Conclusion

Podophyllin cautery, when added to surgical removal, is effective in decreasing the incidence recurrence in cases with CA. Also, this combination is safe for those cases on the long run.

Compliance with Ethical Standards

Declaration of Interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research bioethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the

study.

Declaration of Conflict of Interests

All authors have no things to disclose.

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