Objective: We attempted to evaluate the therapeutic effect of trichloroacetic acid (TCA) for vaginal intraepithelial neoplasia (VaIN) after hysterectomy and to identify factors affecting persistence/recurrence.

Methods: Twenty-eight post-hysterectomy patients with various grades of VaIN were enrolled in this study between January 2001 and December 2003. They were managed with intravaginal 50% TCA once weekly for 1–4 weeks, and all patients were followed up every 3 months for at least 1 year. Assessments by Papanicolaou smear and colposcopy were performed, as was biopsy when indicated during the follow-up period. Cox regression analysis was used to identify independent factors predicting persistence/recurrence.

Results: In 20 of 28 patients (71.4%) VaIN went into remission. Treatment success was observed in all 11 patients with VaIN I, whereas only 9 out of 17 patients (53%) with VaIN II/III went into remission (P = 0.009). Severity of VaIN was the only significant independent predictor of persistence/recurrence (odds ratio = 3.5; 95% confidence interval = 1.1, 11.6; P = 0.038). The treatment was well tolerated with no major side effects.

Conclusions: Based on our findings, 50% TCA was a potential agent with minimal side effects for low-grade VaIN. Further prospective controlled study is warranted to verify our statements. However, as for high-grade lesions, further investigation with different TCA concentration is compelling.

Key words: trichloroacetic acid – vaginal intraepithelial neoplasia – hysterectomy

INTRODUCTION

Vaginal intraepithelial neoplasia (VaIN) is much less common than cervical or vulvar dysplasia. VaIN may occur as an isolated lesion, but is more commonly seen as a lesion developing on the vaginal vault after hysterectomy in patients with cervical intraepithelial neoplasia (CIN) or invasive carcinoma. Owing to the potential persistence and progression of VaIN to invasive cancer (1), successful management of the disease is compelling.

Current treatments for VaIN include surgical excision, laser ablation and topical applications of therapeutic agents. Surgical excision has been reported to be the most effective mode of treatment, however, its use in treating multifocal lesions is still being debated (2,3). Although carbon dioxide laser ablation offers the advantage of treating large and multifocal lesions, it is comparatively high-cost and faculty-dependent.

Topical applications of 5-fluorouracil (5-FU) have been widely used for the treatment of VaIN with varying degrees of success; it is convenient to apply and technically uncomplicated. The greatest disadvantage of topical 5-FU therapy is that it may lead to troublesome chronic mucosal ulcers (4).

Trichloroacetic acid (TCA) CCl₃COOH, made by chlorinating acetic acid, is often used as a laboratory reagent but its main use is in the production of its sodium salt, which is used in many industries, for example, as an herbicide, etching agent and antiseptic. TCA is also a powerful keratolytic agent that can coagulate proteins of the skin, killing all living structures to the level of the reticulary dermis. Therefore, TCA is widely utilized for the treatment of cutaneous hyperpigmentations and fine wrinkling (5). It has also been shown to have a therapeutic effect on genital warts and human papillomavirus (HPV) infection (6,7). Based on these results, it would be worthwhile to use this agent to treat intraepithelial neoplasia. The purpose of the present study, therefore, was to assess the therapeutic effect and toxicity of topical 50% TCA for VaIN following hysterectomy, and to identify the factors affecting persistence/recurrence.

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METHODS
Between January 2001 and December 2003 at Kaohsiung Chang Gung Memorial Hospital, 28 post-hysterectomy patients with histologically confirmed VaIN of any grade were enrolled in this observational study. All of the 28 patients were diagnosed based on a histologic specimen taken by colposcopically directed biopsies. In our hospital, 50% TCA was prepared by adding water to 50 gm of TCA crystals until 100 ml of solution was reached. After informed consent was obtained, 50% TCA was offered intravaginally to these 28 women. Briefly, the vagina was exposed initially using a bivalve speculum. Solutions of 50% TCA were then applied with a cotton ball to the entire vagina until the mucosa turned white. A dry swab was then used to remove any unreacted acid. Treatment was accomplished on an outpatient basis and any subjective complaints were documented during the treatment period.

All 28 patients were asked to come in for reexamination at 1 week intervals in the first month, and 50% TCA was re-applied up to a maximum of four times based on the care-providing physicians’ preference. The patients were then followed up every 3 months after the last treatment with a Papanicolaou smear. When cytological reports showed any abnormality suspicious of disease persistence or recurrence, the patients were assessed colposcopically and a histological confirmation was obtained. Patients with histologically confirmed persistent or recurrent disease were advised to be re-treated with topical 50% TCA, and were informed at the same time regarding the possibility of treatment failure.

For the purpose of this analysis, the effects of age, previous disease, hysterectomy type, number of TCA applications and the severity of VaIN during a disease-free duration were examined. Univariate analysis was performed using the log-rank test, and multivariate analysis was calculated based on the Cox proportional hazards model. A P-value of <0.05 was considered statistically significant.

RESULTS
The ages of the patients ranged from 41 to 78 years, with an average of 59 years. All had a previous history of hysterectomy. Eleven patients (39%) had received radical hysterectomy with pelvic lymphadenectomy owing to early invasive cervical carcinoma, 13 patients (47%) had undergone a simple hysterectomy owing to CIN Grade III, whereas the remaining four patients (14%) had a simple hysterectomy owing to a benign uterine neoplasm. Four of the 28 patients also had a previous history of pelvic radiation as a post-operative adjuvant therapy for cervical carcinoma. As for the VaIN lesions, 11 patients (39%) were VaIN Grade I, 5 (18%) were VaIN Grade II and 12 (43%) were VaIN Grade III. The distribution of VaIN lesions varied from single to multifocal but all located over upper two-third of vagina. The characteristics of the patients are summarized in Table 1.

<table>
<thead>
<tr>
<th>Causes of hysterectomy</th>
<th>Types of hysterectomy</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical carcinoma</td>
<td>RAH + BPLND</td>
<td>11</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>CIN Grade III</td>
<td>Simple hysterectomy</td>
<td>13</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Benign uterine neoplasm</td>
<td></td>
<td>4</td>
<td>24</td>
<td>28</td>
</tr>
</tbody>
</table>

The median follow-up time was 23 months, ranging from 12 to 30 months. The lesions went into remission in 20 of 28 patients (71.4%). Twelve patients received a single treatment, 11 patients 2 weeks’ treatment, 4 patients 3 weeks’ treatment and 1 had treatment for 4 weeks. Treatment success was observed in all the 11 patients (100%) with VaIN Grade I, whereas only 9 out of 17 patients (53%) with VaIN Grade II/III went into remission, which was statistically significant (P = 0.009; log-rank test; Fig. 1). Univariate analysis of factors associated with disease persistence/recurrence was summarized in Table 2. Cox regression analysis showed that age, previous disease, type of previous hysterectomy and number of TCA applications were not related to treatment failure; only the severity of VaIN was found to be a significant variable predicting disease persistence/recurrence (odds ratio = 1.1, 11.6; = 0.038, Table 3). Disease in the eight patients whose treatment failed reappeared within 1 year after the initial treatment. No patients progressed to invasive carcinoma. Four of them decided to re-treat the disease with 50% TCA topically after full consultation, including the possibility of treatment failure, two patients refused further treatment and followed up expectantly, and two patients were not advised to re-treat owing to the appearance of metastatic lesions outside the vagina from their primary cervical carcinoma. Fortunately, three of the four patients (75%) responded to a re-application of 50% TCA and achieved remission with a median follow-up of 12 months.

The treatment was well tolerated with minimal side effects. All 28 patients experienced a burning sensation in the vagina, but only one patient needed an oral analgesic for symptom
relief. A reddish change in the vaginal mucosa was observed in all the patients at the site of application during the treatment period. However, there were no long-term TCA-related vaginal mucosal alterations.

**DISCUSSION**

Several published investigations have proved that TCA can damage HPV DNA to a certain degree at different concentrations (7–9). However, no report has been published to date regarding its therapeutic effect in treating intraepithelial neoplasia. We demonstrated an excellent result using topical 50% TCA in treating low-grade VaIN following hysterectomy, with minimal side effects. Although its effect in the treatment of high-grade VaIN was modest in our results, 50% TCA seemed to have the ability to slow down the progression of the major intraepithelial lesions.

One might point out that most of the low-grade VaINs can regress spontaneously without any treatment. Aho et al. (1) reported that 78% of VaINs may regress, 13% may persist and the remaining 9% may progress to invasive vaginal carcinoma. In the study reported by Rome et al. (10), the results showed that 12% of patients with low-grade VaIN had the potential to progress if left untreated. Therefore, it is assumed that VaIN progresses to invasive disease similar to that of CIN. However, the exact malignant potential of VaIN is still not known, and it is difficult to determine whether the lesions will indeed progress (11). We believe that it is unnecessary to treat low-grade VaIN if the mode of treatment is invasive and potentially risky, but is reasonable and worthwhile to treat if the benefits of the treatment, such as non-invasiveness, low cost and easy application outweigh its disadvantages. Our results showed that the high efficiency of intravaginal 50% TCA fairly well matched its minimal side effects in treating low-grade VaIN. However, the only drawback of our study is that there is no control group and VaIN I may regress spontaneously without treatment. Therefore, it is very difficult to observe the actual effect of 50% TCA for VaIN I in our patients. Further prospective controlled study, with one arm treat with 50% TCA and the other arm treat with normal saline, is warranted to verify our results.

As for high-grade VaIN, several types of treatment have been reported, including surgical excision, laser ablation, electrocoagulation diathermy, cavitation ultrasonic surgical aspiration, high-dose rate intracavitary brachytherapy and topical 5-FU cream. The results have been inconsistent, with the success rates ranging from a low of 25% to a high of 100% (10,12–15). Among the various types of treatment, surgical excision, laser ablation and radiotherapy are considered to be the most effective. The advantage of surgical excision over the others is that it can provide tissue to submit for histological examination, and thus occult invasive foci cannot
be missed (12). However, surgical excision and laser ablation require general anesthesia and carry the risk of adjacent organ injury during treatment (16). Radiotherapy, however, carries the risk of a subsequent development of neoplasia owing to low-dose radiation exposure; moreover, it is generally not suitable for pre-irradiated patients (17). Topical application of 5-FU cream has been widely used; it is easy to apply, does not require anesthesia and can be performed on an outpatient basis. The success rates have varied, ranging from 41 to 93% (2,18). The wide discrepancy might be related to the differences in the interval and duration of treatment. The major complication was chronic vaginal mucosal ulcers. Krebs and Helmkamp (4) reported an 8.2% incidence of troublesome ulcers, and spontaneous healing was impossible. All the patients with chronic vaginal mucosal ulcers in their study required excision and primary closure. We demonstrated a novel treatment without any major adverse effects using topical TCA. The relatively low success rate (53%) in our study might be owing to an inadequate concentration of TCA since the depth of tissue damage increased with the concentration of TCA (19). Although our follow-up was short, the majority of the previous studies documented a mean time to recurrence of <1 year (20). In a follow-up trial, we are using a more concentrated TCA treatment with different numbers of applications, and evaluating its therapeutic and adverse effects with this concentration.

We have drawn the conclusion that 50% TCA is a potential agent in the treatment of low-grade VaIN following hysterectomy, and that it offers, as well, the advantages of low costs, no secondary effects, and an easy application and handling. The use of this relatively inexpensive and low-tech approach would be of great advantage for those patients with persistent low-grade VaIN, particularly in resource-limited developing countries. Further prospective controlled study is warranted to verify our results. In patients with high-grade lesions, the therapeutic effect of TCA needs further investigation including the use of different TCA concentration.

References