Original Research

Short-Term Efficacy of Trichloroacetic Acid in the Treatment of Cervical Intraepithelial Neoplasia

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OBJECTIVE: To establish the short-term efficacy and tolerability of a single topical 85% trichloroacetic acid treatment for cervical intraepithelial neoplasia (CIN) 1–3.

METHODS: A retrospective case series including all patients with CIN treated with trichloroacetic acid as first-line therapy was performed. Treatment response was evaluated by colposcopy, cervical biopsy, cytology, and type-specific human papillomavirus (HPV) testing 8 weeks after a single trichloroacetic acid treatment. Regression was defined as improvement from high-grade to low-grade CIN and remission was defined as improvement from any grade of CIN to no CIN. For quantification of treatment-related pain, 107 (44.1%) patients rated their subjective perception on a visual analog scale.

RESULTS: A total of 241 women were included in the study with 179 high-grade (CIN 2–3) and 62 low-grade (CIN 1) squamous intraepithelial lesions. For high-grade squamous intraepithelial lesions, the histologic regression rate was 87.7% (95% confidence interval [CI] 82.0–92.1) and the remission rate was 80.3% (95% CI 73.3–85.5). For low-grade squamous intraepithelial lesions, the remission rate was 82.3% (95% CI 70.5–90.8). Human papillomavirus types 16 and 18 were found in 53.7% and 7.3% of all women tested, respectively. Clearance rates of HPV type 16 and HPV type 18 were 73.5% (95% CI 62.5–81.3) and 75.0% (95% CI 46.2–95.0), respectively. Median pain score was 3.0 out of 10.0 (25th and 75th percentiles 2.3 and 4.3, respectively). There were no major side effects observed during treatment or follow-up.

CONCLUSION: A high regression and remission rate and a high HPV clearance rate were observed 8 weeks after topical 85% trichloroacetic acid treatment for patients with CIN.

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Management of cervical intraepithelial neoplasia (CIN) varies significantly by grade, underlying human papillomavirus (HPV) type, and patient's age. Conservative management is preferred for low-grade CIN and for CIN in women younger than 25 years of age, because these lesions are frequently transient in nature.[1] Abnormal screening results are often associated with emotional distress. Women under active surveillance experience anxiety and uncertainty about having cancer while waiting for the follow-up visit.[2]

Surgical management most frequently with loop electrosurgical excision procedure is preferred for high-grade CIN and persistent or recurrent CIN, showing efficacy rates ranging from 90% to 95% and a low rate of short-term adverse effects.[1,3,4] However, a significant long-term side effect of conization seems to be an increased risk for preterm birth.[5–7] To circumvent complications from both, surgical and conservative management alternative treatment options for CIN are desired.

Topical 85% trichloroacetic acid represents a promising nonsurgical approach in managing cancer precursors because it is inexpensive, well tolerated, has no systemic side effects, and is safe to use during pregnancy.[8–10] Trichloroacetic acid causes protein

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denaturation and cell death.[11] It is widely used for cosmetic treatments and has shown to be an effective treatment for condylomata acuminate.[9] In terms of premalignant lesions, trichloroacetic acid proved to be an efficient therapy for anal intraepithelial neoplasia and vaginal intraepithelial neoplasia.[10,12]

The efficacy of topical 85% trichloroacetic acid as first-line treatment for CIN is unknown. The aim of this study was to establish the short-term efficacy and tolerability of a single topical 85% trichloroacetic acid treatment for CIN 1–3.

MATERIALS AND METHODS

This retrospective study included all women undergoing trichloroacetic acid treatment between September 2012 and January 2015 at a private colposcopy clinic associated with the Department of General Gynecology and Gynecological Oncology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria. The institutional review board of the Medical University of Vienna approved the study (institutional review board No. 1905/2014). Women eligible for trichloroacetic acid treatment had biopsy-confirmed CIN 1, which had persisted for a minimum of 6 months, or CIN 2–3. Patients refusing biopsy requesting a "see and treat" approach were eligible based on cytologically suspected CIN (low-grade squamous intraepithelial lesions [LSIL] or high-grade squamous intraepithelial lesions [HSIL]) if there were no signs of invasion on colposcopy. For all patients a satisfactory colposcopy (ie, fully visible transformation zone and a clearly to endocervical demarcated lesion) and agreement to follow-up was mandatory. Women with LSIL or HSIL but an inadequate colposcopy or negative histology were not eligible for trichloroacetic acid treatment. All patients considered for trichloroacetic acid treatment were informed that conization is the current treatment of choice for moderate to severe CIN.[13] From January 2014 onward, patients were asked to report their subjective pain on a visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst possible pain) immediately after the trichloroacetic acid treatment.

At the screening and follow-up visit, cervical cytology (ecto- and endocervix) and a type-specific HPV test were obtained and colposcopy with 3% acetic acid was performed. At the screening visit a colposcopically guided biopsy of any visible lesion was recommended to all patients if not previously taken at an earlier examination. All cytologic and histologic specimens were analyzed by one board-certified pathologist specialized in gynecologic pathology. In patients with a "see and treat" approach, the day of the screening corresponded with the day of treatment. Patients were advised not to have sexual intercourse for 2 weeks, to choose showering over bathing for 4 weeks, and to use sanitary pads rather than tampons during menstruation. The follow-up visit was scheduled for 8 weeks after the trichloroacetic acid treatment. A colposcopically guided biopsy and an endocervical curettage were strongly recommended to all patients. Furthermore, reepithelialization of the cervical surface was assessed. If the original lesion was no longer visible at colposcopy, a random biopsy form each of the four quadrants of the cervix was performed. To asses side effects at the follow-up visit, patients were specifically asked for vaginal discharge or bleeding, postcoital bleeding, signs of pelvic inflammatory disease, the need for medical treatment, and were asked to report any other possibly treatment-related symptoms.

Trichloroacetic acid is a clinician-applied treatment and was applied by only one investigator (P.S.). In this study 85% trichloroacetic acid was used for treatment. A small cotton swab was saturated with trichloroacetic acid and applied to the ectocervix. A thin layer was applied to the ectocervix and transformation zone and allowed to turn white, indicating precipitation of denatured proteins[14] (Fig. 1). Trichloroacetic acid has low viscosity; therefore, care was taken because it can easily drip down onto normal tissue, which can also become chemically coagulated. To treat the caudal part of the cervical canal, the wooden stick end of the cotton swab was dipped into trichloroacetic acid and when saturated applied (Fig. 1).

Patients with normal colposcopy, negative histology and cytology, and complete HPV clearance were recommended to have their next Pap test in 12 months. In cases with type-specific HPV persistence as the only positive result, repeated HPV testing was recommended in 3–6 months. In patients with type-specific HPV persistence of 16 or 18, deep endocervical curettage reaching as high up as to the internal os of the cervical canal was performed after injection of local anesthetic (lidocaine HCL 2% and epinephrine 1:100.000) into the cervical stroma. If the initially described lesion had not cleared at the 8-week follow-up, patients received standard therapy and the trichloroacetic acid treatment was not repeated, because there is currently insufficient evidence on the safety of repeated applications.

Histologic regression (from high-grade to low-grade CIN), complete remission (from any grade of CIN to no CIN) at 8 weeks after topical application of 85% trichloroacetic acid, and type-specific HPV

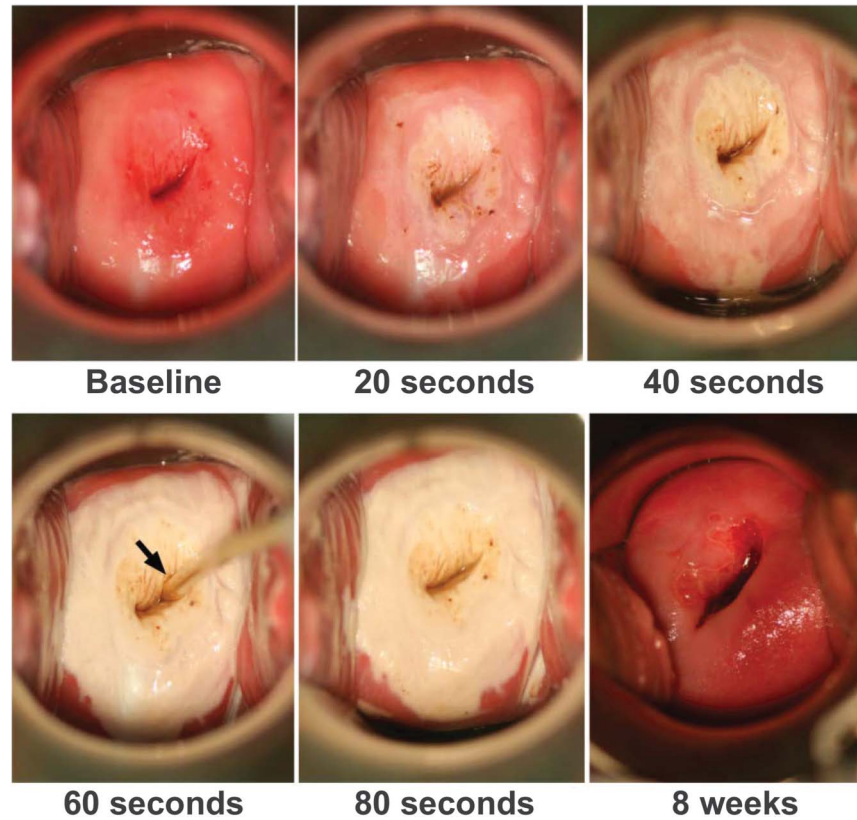

Fig. 1. Treatment of high-grade cervical intraepithelial neoplasia (CIN) with topical 85% trichloroacetic acid. The first (baseline) photograph was taken after the application of 3% acetic acid. The photographs at the time of 20, 40, 60, and 80 seconds were taken after the application of 85% trichloroacetic acid. The photograph at 60 seconds shows the treatment of the endocervical canal with the wooden end of a cotton tip (*arrow*) saturated with 85% trichloroacetic acid. The final photograph was taken 8 weeks after treatment.

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clearance for types 16 and 18 were described by proportions and 95% Clopper-Pearson-type exact confidence intervals. Treatment tolerability was interpreted according to VAS and described by median and interquartile range. The study was powered to detect a remission rate significantly higher than 50% assuming the true remission rate was 59% or higher (two-sided α 5%, power 80%).

The statistical analysis was based on the intention-to-treat principle, that is, all patients included were also incorporated in the evaluation. Women with missing data on remission or regression of CIN and HPV clearance resulting from refusal to continue participation, and those who failed to appear at scheduled follow-up visits, were regarded as nonresponders.

RESULTS

In total 241 patients with CIN 1–3 were included in this study. The median age of all women included was 31 years and the 25th and 75th percentiles were 26 and 35, respectively. Baseline characteristics are provided in Table 1. The study population was divided in two groups: high grade (HSIL on cytology, CIN 2–3 on histology, or both) and low grade (LSIL on cytology, CIN 1, or both). If available, patients were grouped based on cervical biopsy result. Patients refusing biopsy were grouped based on the cervical cytology. In 15 (8.4%) patients with high-grade lesions and seven (11.3%) with low-grade lesions, HPV typing was not available before trichloroacetic acid treatment. A cohort of 21 patients (16 from the high-grade group and five from the low-grade group) with normal colposcopy and negative cytology refused biopsy at the follow-up visit. These patients were grouped based on cervical cytology. In one patient with a high-grade lesion at study entry, both histology and cervical cytology were missing at the follow-up visit and was therefore entered into the nonremission group according to the intention-to-treat principle.

Histologic regression and remission rate and HPV clearance rate were assessed 8 weeks after a single trichloroacetic acid treatment. In the group of patients with high-grade lesions, histologic regression and remission rate were 87.7% (95% confidence interval [CI] 82.0–92.1) and 80.3% (95% CI 73.3–85.5), respectively (Table 2). Histologic remission rate in the group of patients with low-grade lesions was 82.3% (95% CI 70.5–90.8) (Table 2). In the group of patients who had at both time points (screening visit

Table 1. Patients' Characteristics at Study Inclusion

Characteristic	Value
Total N	241
Age (y)	31 (26, 35)
Lesion grade*	241
Low grade	62 (25.7)
High grade	179 (74.3)
Histology	190
CIN 1	34 (17.9)
CIN 2	71 (37.4)
CIN 3	85 (44.7)
Cytology	236
Normal	17 (7.2)
ASC-US	2 (0.9)
LSIL	124 (52.5)
HSIL	93 (39.4)
High-risk HPV	218
16	117 (53.7)
18	16 (7.3)
Other	85 (39.0)

CIN, cervical intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; HPV, human papillomavirus.
Data are n, median (25th, 75th percentile), or n (%).
* Patients were grouped primarily on biopsy results; patients refusing biopsy were grouped according to cervical cytology results.

and follow-up) biopsy results available, remission and regression rates were calculated separately (Table 3). Human papillomavirus clearance for HPV type 16, HPV type 18, and all high-risk HPV types after a single trichloroacetic acid treatment was 73.5% (95% CI 64.6–81.2), 75% (95% CI 47.6–92.7), and 62.8% (95% CI 56.1–69.3), respectively (Table 4). A flow diagram is provided (Figs. 2 and 3).

Table 2. Histopathologic or Cytologic Responses or Both of High-Grade and Low-Grade Cervical Intraepithelial Neoplasia 8 Weeks After a Single Topical Treatment With 85% Trichloroacetic Acid

Lesion Grade	n*	Regression†	Remission‡
High	179	157 (87.7)	143 (80.3)
95% CI		82.0–92.1	73.3–85.5
Low	62	N/A§	51 (82.3)
95% CI		N/A	70.5–90.8

CI, confidence interval; N/A, not applicable.
Data are n (%) unless otherwise specified.
* Patients were grouped based on cervical biopsy; patients refusing biopsy were grouped based on the cervical cytology.
† Regression is defined as improvement from high grade to low grade (ie, cervical intraepithelial neoplasia [CIN] 3 becomes CIN 1 or 2, and CIN 2 becomes CIN 1).
‡ Remission is defined as complete histologic remission (ie, CIN of any grade becomes normal).
§ Low-grade regression=remission.

Table 3. Histologic Response Rate of Cervical Intraepithelial Neoplasia 1–3 8 Weeks After a Single Topical Treatment With 85% Trichloroacetic Acid

CIN Grade*	n	Regression†	Remission‡
1	32	N/A§	24 (75.0)
95% CI		N/A	56.6–88.5
2	61	56 (91.8)	51 (83.6)
95% CI		81.9–97.3	71.9–91.9
3	79	71 (90.0)	62 (78.5)
95% CI		81.0–95.5	67.8–86.9

CIN, cervical intraepithelial neoplasia; N/A, not applicable.
Data are n (%) unless otherwise specified.
* Patients with biopsy result at both inclusion and follow-up.
† Regression is defined as improvement from high-grade to low-grade.
‡ Remission is defined as complete histologic remission.
§ CIN 1 regression=remission.

There were no major side effects such as heavy vaginal bleeding or admission to the hospital observed during treatment and follow-up. A total of 107 (44%) patients reported their subjective pain on VAS immediately after the trichloroacetic acid treatment. The median score was 3.0 (interquartile range 2.3–4.3). Only one patient presented with vaginal bleeding before her scheduled follow-up visit. Bleeding was minimal and did not require any intervention. In one case a patient required telephone counseling and vaginal treatment with an antiseptic lotion initiated for an offensive discharge. Postcoital bleeding was not reported at all. Vasovagal symptoms (eg, lightheadedness) during and immediately after treatment were observed in 17 patients (7.1%), affecting mostly young, nulliparous women, with one patient experiencing syncope. At the follow-up visit reepithelialization of the ectocervix was incomplete in nine (3.7%) patients. A progression from CIN to cancer was neither observed during the study nor thereafter.

DISCUSSION

Our study demonstrates that by chemical coagulation of proteins, a single treatment of topical trichloroacetic acid for CIN 1–3 is associated with a major response and high HPV clearance rate 8 weeks after treatment. There was no major difference between high-grade and low-grade CIN with remission rates of 80.3% and 82.3%, respectively. The effectiveness of trichloroacetic acid treatment did not appear to be dependent on HPV type. Treatment was well tolerated with a median VAS score of 3.0 without

Table 4. Human Papillomavirus Clearance 8 Weeks After a Single Topical Treatment With 85% Trichloroacetic Acid

Lesion Grade*	HPV Type 16	HPV Type 18	All High-Risk HPV Types†
High	95	13	163
Clearance	69 (72.6)	10 (76.9)	104 (63.8)
95% CI	62.5–81.3	46.2–95.0	55.9–71.2
Low	22	3	55
Clearance	17 (77.3)	2 (66.7)	33 (60.0)
95% CI	54.6–92.2	9.4–99.1	45.9–73.0
Total	117	16	218
Clearance	86 (73.5)	12 (75.0)	137 (62.8)
95% CI	64.6–81.2	47.6–92.7	56.1–69.3

HPV, human papillomavirus; CI, confidence interval.
Data are n or n (%) unless otherwise specified.
* Patients with both HPV test at inclusion and follow-up.
† Patients with one or more HPV high-risk types, including HPV types 16 and 18.

use of local anesthesia. For comparative reasons, median VAS score for peripheral intravenous cannula insertion with or without lidocaine cream was reported to be 3.0 and 7.0, respectively.[15] No major side effects were observed during treatment and follow-up. This contrasts with established treatments for CIN, in which such complications occur in a significant minority of patients.[4]

The efficacy of local application of trichloroacetic acid for the treatment of anal intraepithelial neoplasia has been demonstrated and is recommended for the treatment of small lesions, which compares very well to our results.[16] Trichloroacetic acid treatment was studied in 72 men who tested positive for human immunodeficiency virus. In this study population, 98 patients with HSIL were treated and 79% of lesions showed complete remission or regression to LSIL, and only a small minority (2%) of patients required more than two treatments.[17] Similar results were observed in a trial of 54 men, of whom 35 (64.8%) were human immunodeficiency virus-positive.[10] In both studies patients were not prescribed analgesia or anesthesia and reported that treatment-related side effects were minimal.

In-depth experiences with trichloroacetic acid treatment in gynecology are mostly restricted to the treatment for condyloma acuminate.[17] Furthermore, trichloroacetic acid treatment of HPV infection of the cervix without dysplasia was reported with conflicting results. In a study reported by Malviya et al,[18]

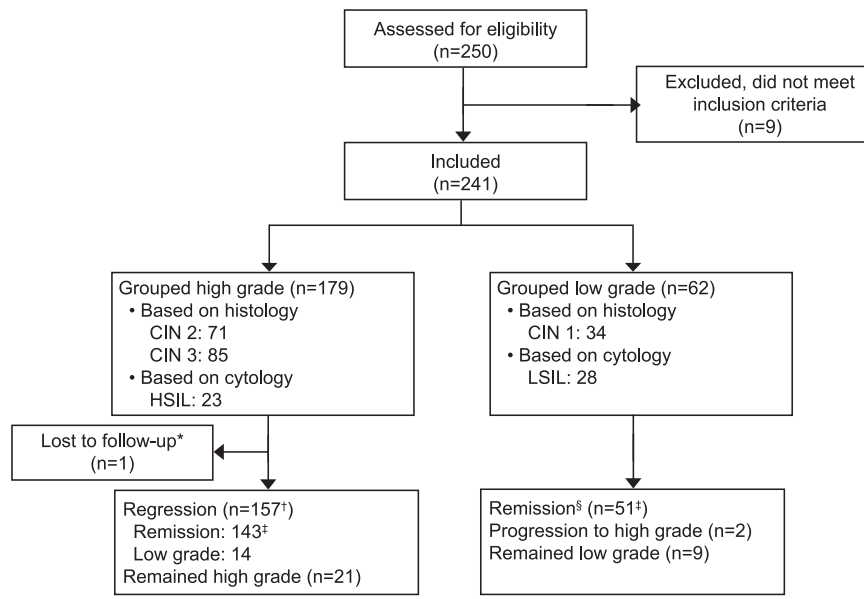

Fig. 2. Flow diagram of study population, baseline characteristics compared with 8-week follow-up. *Patient included in nonremission (remained high grade) group per intention-to-treat principles. †Regression is defined as improvement from high grade (cervical intraepithelial neoplasia [CIN] 2–3, high-grade squamous intraepithelial lesions [HSIL]) to low grade (CIN 1, low-grade squamous intraepithelial lesions [LSIL]) or back to normal (therefore, every remission is also a form of regression). ‡Remission is defined as complete histologic remission (ie, CIN of any grade becomes normal). §Low-grade regression equals remission.

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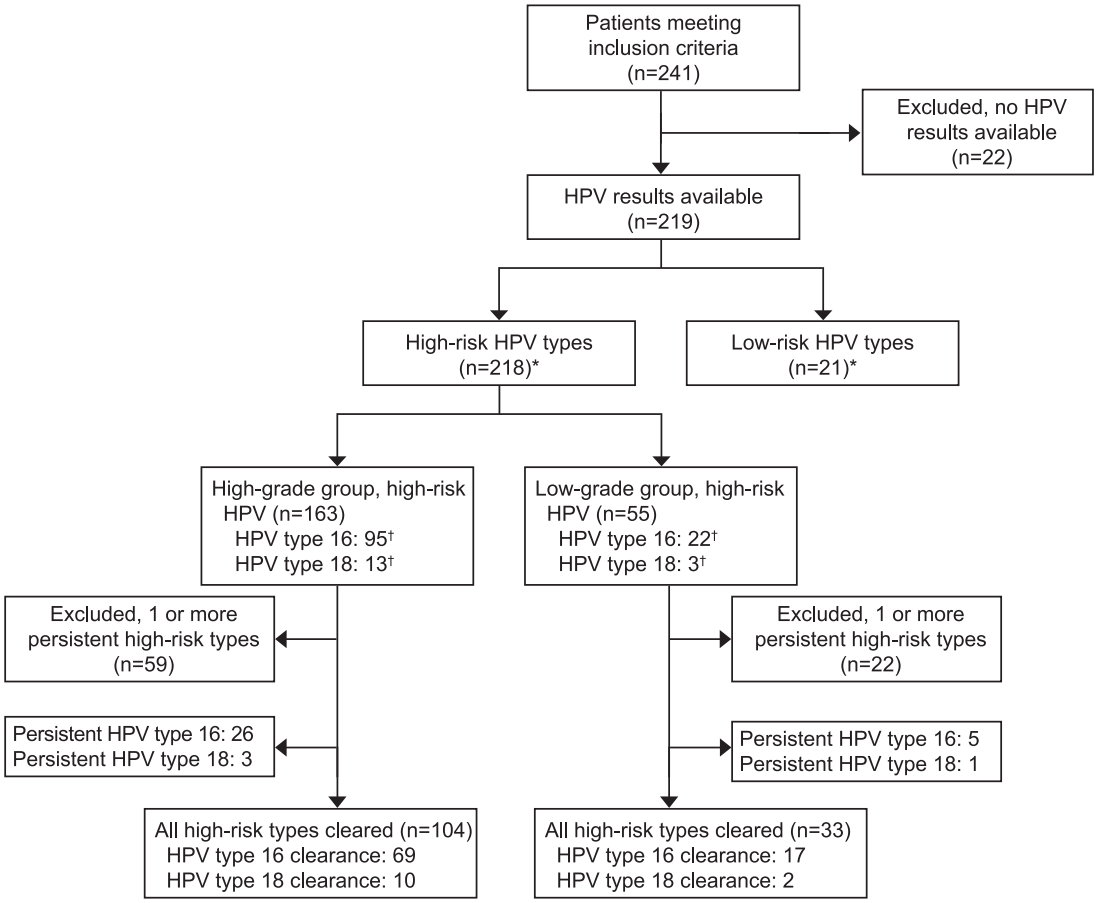

Fig. 3. Flow diagram representing human papillomavirus (HPV) status, baseline characteristics compared with 8-week follow-up. *Two hundred eighteen patients tested positive for high-risk HPV types, 20 patients had a combination of high-risk and low-risk HPV types, and one patient only had low-risk HPV types. †Values do not add up to the n value, because various distributions of HPV-type infection were found such as HPV type 16, HPV type 18, other high-risk types, or all of these.

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treatment with 85% trichloroacetic acid of 46 patients with HPV infection of the cervix resulted in HPV clearance in 81.6% at 3 months follow-up. A subsequent randomized, double-blind study in the same population of women applying 50% trichloroacetic acid did not show any differences between the treatment and placebo groups.[19] Treatment of vaginal intraepithelial carcinoma in 28 patients after hysterectomy with 50% trichloroacetic acid was studied, demonstrating a 71.4% remission rate. Treatment was particularly effective in 11 patients with low-grade lesions, all of them going into remission.[12]

There are several other ablative therapies available, which use either heat (cold coagulation, electrocoagulation diathermy, laser coagulation) or cold (cryotherapy with refrigerant gas or liquid nitrogen). All these techniques require specialist equipment and training with all their associated expense and logistic implications. Trichloroacetic acid, because of its ease of use, low cost, and good safety profile, presents a very attractive alternative, which largely circumvents these issues.

Treatment with the immune response modulator imiquimod containing self-applied vaginal suppositories 2–3 times a week for 16 weeks is effective but tedious and morbid.[20] Treatment with 85% trichloroacetic acid is generally well tolerated with a median VAS score of 3.0. Pain usually subsides within minutes after the treatment that takes approximately 3 minutes. One could speculate that nonsteroidal anti-inflammatory drug premedication might improve tolerability even further.

Complication rates after ablative therapy are generally low, approximately 1–2%.[21] Vaginal discharge is the most frequent side effect.[22] Posttreatment bleeding is usually minimal and will resolve with conservative

measures. Pelvic inflammatory disease after ablation for CIN is infrequent.[23] In the present series watery blood-stained discharge was reported frequently, which usually lasted approximately 2 weeks. Because no tissue is removed at the time of ablative treatment of CIN, the presence of invasive disease cannot be excluded, and stringent follow-up is mandatory, because some patients have gone on to develop cancer after ablative treatments.[24] Just like after laser ablation,[22] the squamocolumnar junction usually returns to its pretreatment location and can be visualized after 85% trichloroacetic acid treatment (Fig. 1).

Limitations of our study are the retrospective nature, missing control group, missing data, and that it was done in one single institution. The short-term follow-up does preclude any insight on long-term outcomes. The "see and treat" approach will inevitably result in treatment of cancer with an unknown effect, and safety is yet to be demonstrated. However, despite these limitations of the study, we are unaware of any other reports of using trichloroacetic acid for treatment of CIN.

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