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Effectiveness and safety of ablative Er:YAG laser treatment for external genital warts

Varnost in učinkovitost odstranjevanja genitalnih bradavic z ablativnim erbijevim laserjem

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Abstract

Background: The aim of this study is to evaluate effectiveness and safety of the use of ablative Er:YAG laser for removal of external genital warts (EGW), also called condylomata acuminata (CA).

Methods: This is a retrospective cohort study performed at Gynecology Clinic Juna in Ljubljana, Slovenia. All patients older than 18 years that were clinically diagnosed with EGW and were treated with ablative Er:YAG laser between January 2012 and December 2017 were included in the study.

Results: A total of 133 female patients (mean age 39.6 ± 12.9 years, range: 19–80) with EGW were eligible to be included in this study. EGW have been present from one to seven months, with a mean presence of 2.1 ± 2.0 months. The majority of the warts were on the labia, major some also on the mons pubis. The size of the lesions was 2–8 mm. The majority of patients, who completed therapy (74 patients out of 116; 64) received only one treatment and 82 of the patients (n = 95) showed complete clearance of the lesions, without recurrence observed to date of analysis. Complete clearance was achieved after an average of 1.33 treatment sessions. Recurrence was reported by 21 patients (18). Recorded adverse effects of laser treatment were mild and transient.

Conclusion: Er:YAG laser removal of EGW is a simple, quick and safe procedure, particularly suitable for large volume EGW or those that are located in anatomical sites difficult to access by other techniques.

Izvleček

Izhodišče: Raziskava skuša ovrednotiti učinkovitost in varnost odstranjevanja genitalnih bradavic (kondilomov) z ablativnim erbijevim laserjem.

Metode: Retrospektivna kohortna raziskava je vključevala vse bolnice, starejše od 18 let, pri katerih smo v ginekološki ambulanti Juna v obdobju med januarjem 2012 in decembrom 2017 diagnosticirali genitalne bradavice in jih odstranili z ablativnim erbijevim laserjem.

Rezultati: Skupaj je bilo v raziskavo vključenih 133 bolnic (povprečna starost: 39,6 ± 12,9, razpon let: 19–80). Pri bolnicah so bile genitalne bradavice prisotne od enega do sedmih mesecev, v povprečju 2,1 ± 2,0 meseca. Večinoma so se nahajale na velikih sramnih ustnicah, v nekaterih primerih tudi na nadsramju. Velikost bradavic je bila med 2 in 8 mm. Pri večini bolnic (74 od 116, 64 %) je bil potreben le en poseg z laserjem. Pri 82 % bolnic (n = 95) je bilo zdravljenje uspešno in ponovnega pojava genitalnih bradavic nismo zaznali, pri čemer smo v povprečju za popolno

odstranitev genitalnih bradavic potrebovali 1,33 posega. Pri 21 osebah (18 %) je prišlo do ponovnega izbruha genitalnih bradavic. Opaženi stranski učinki laserskega posega so bili blagi in prehodni.

Zaključek: Odstranjevanje genitalnih bradavic z ablativnim erbijevim laserjem je enostavno, hitro in varno, še posebej primerno pri obsežnih spremembah, ki se nahajajo na težko dostopnih anatomskih mestih.

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1 Introduction

Human Papillomavirus (HPV) is a highly contagious virus that is the cause of one of the most frequently transmitted viral infections in the world (1,2). HPV infection is spread by skin-to-skin contact, predominately during sexual activity, and is therefore considered a sexually transmitted infection (STI) (1). There have been more than 200 HPV genotypes identified, approximately 40 of which are capable of infecting the anogenital tract and are categorized as either low or high risk, based on their capacity of inducing malignancy (3,4). External genital warts (EGW), also called condylomata acuminata, are benign cellular proliferations of the anogenital skin and mucosa that form in response to viral infection with a low-risk HPV genotype, usually types 6 or 11 (4,5). Pre-exposure vaccination in the form of either bivalent, quadrivalent or 9-valent vaccine is one of the most effective methods for preventing infection and transmission of the virus and has been recommended by the WHO as part of routine vaccination since 2007 (6).

Most (70–90%) of HPV infections are asymptomatic and can resolve spontaneously, however, once EGW develop, the treatment options are directed toward removal of the warts and usually do not eliminate the HPV infection (4). The available treatments are highly variable with respect to their cost, side-effect profile, dosing schedules, treatment duration, overall effectiveness and availability to patients (4). They can be grouped into topical interventions and physical ablative techniques, including laser vaporisation (7). Laser vaporisation is performed using ablative lasers, which are highly absorbed in water and can vaporise structures on the tissue surface. The most frequently used laser for vaporisation of EGW has been the CO_2 laser, because of its established use in gynaecological surgery. However, there are lasers that are even more highly absorbed in water and these could therefore present an even better solution for surface vaporisation. The Er:YAG laser has a wavelength of 2940 nm and has a ten times higher optical absorption coefficient in tissue water than the CO_2 laser. This results in cleaner and more precise target tissue removal with minimal adjacent tissue damage (8). It has also been shown that the Er:YAG laser plume resulting from EGW treatment is free of HPV DNA (9), however, the use of an evacuation hood is recommended when performing any ablative laser procedure.

Er:YAG has been widely and successful-

ly applied for treatment of common warts (10-13), however, literature describing the use of Er:YAG for treatment of EGW is scarce (11,14). The aim of this paper was to retrospectively analyse the effectiveness of Er:YAG laser vaporisation of EGW in cases from our clinical practice.

2 Materials and Methods

2.1 Study design and patient population

This was a retrospective chart review study that was conducted at the Gynecology Clinic Juna, Ljubljana, Slovenia. Ethics approval (No. 0120–253/2019/7) was obtained from the National Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia and the study was conducted according to the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT04073082). The aim of this study was to retrospectively evaluate the effectiveness and safety of Er:YAG laser for treatment of EGW in patients treated in our clinic during six years of clinical practice.

All female patients older than 18 years that were clinically diagnosed with EGW and were treated with Er:YAG laser between January 2012 and December 2017 were included in the study. Eligible patients were followed from the initial diagnosis until the most recent chart entry. The following parameters were relevant for our chart review: general demographic data; medical history; previous treatments; number of laser treatments needed for lesion clearance; laser parameters used; and adverse effects of laser treatment. In all patients, evaluation of treated lesions was done two weeks following the initial laser treatment. In some cases where the lesions were extensive, more than one treatment was required to completely clear the primary lesion. For these patients, laser treatments were performed every two weeks until the area was completely cleared and asymptomatic. An EGW episode was considered as resolved (clinical clearance) when no recurrence of lesions was observed after six months. All adverse events attributable to laser treatment were noted and followed.

2.2 Laser procedure

EGW were removed using an ablative Er:YAG laser (SP Dynamis, Fotona, Ljubljana, Slovenia). Treatment protocol was comparable in all patients. After routine sterilization of the area, the local anaesthetic was applied (EMLA Cream 5%, Aspen Pharma Trading Ltd., Dublin, Ireland). Laser parameters that were used were adapted to the EGW size and ranged from 2–4 mm spot size (full spot, R11 handpiece), MSP pulse duration (100 µs), with a repetition rate of 3–5 Hz and fluences from 3–5 J/cm^2. Depending on the extent of the lesion, the duration of treatment usually lasted between 15 and 30 minutes. Due to potentially hazardous laser plumes, the practitioner wore a mask with a particle filter, and a fume extractor was used in the treated area. Post-laser care recommendations included careful washing with mild intimate washing gel and sexual abstinence until the treated tissue was completely re-epithelialized.

2.3 Treatment evaluation

The number of treatments needed and possible recurrence were evaluated for each patient. In cases involving extensive lesions, the number of sessions needed to treat the whole area was recorded. Relapse time was determined in accordance with studies using other destructive or surgical approaches, such as cryosurgery and CO_2 laser (4). If the time between consecutive treatments was greater than 1 month, it was considered as a wart recurrence. The effectiveness of Er:YAG laser therapy was defined as the proportion of those patients who had received single treatment or multiple treatments within a period of 30 days (one month) and had no subsequent epi-

sode of EGW. Patient charts were required to have follow-up information available for at least 6 months (180 days) subsequent to their last treatment session. Patients who did not meet this criterion are presented separately and their treatment is being considered as continued at the time of analysis.

2.4 Statistical analysis

Descriptive statistics were calculated for all study variables, including mean, median, standard deviation, and 95% confidence interval (CI) of the mean for continuous variables. Categorical variables were described as absolute and relative frequency over the total valid values (n). Categorical variables were compared using the chi-square test for homogeneity of the groups and ANOVA was used for comparison of the means of continuous variables. The statistical analysis was performed using SPSS software (SPSS ver. 23, IBM SPSS Statistics IBM Corp., NY).

The cumulative risk of subsequent EGW was calculated as the proportion of patients having at least one subsequent episode.

3 Results

3.1 Demographics and patient characteristics

A total of 133 women with EGW were found eligible to be included in this retrospective study (Table 1). Seventeen patients had their last visit recorded within 6 months prior to the data collection, which rendered their therapy incomplete at the time of analysis, whereas 116 patients completed their therapy.

The mean age of patients included in our retrospective chart review is presented in Table 1. Regarding the history of EGW, as reported by patients, they were present from 1 to 7 months, with a mean presence of 2.1 ± 2.0 months. The majority of the genital warts were situated on the labia majora and some on the mons pubis. Size of the lesions ranged from 2 to 8 mm.

Previously received treatments reported by the patients were CO_2 laser, cryotherapy, electrocautery and imiquimod cream.

Table 1: Description of the patient population. The table includes analysis of all patients, and subanalyses of patients who have either completed their therapy or their therapy is continued.

	All patients (n = 133)	Completed therapy (n = 116)	Continued therapy (n = 17)
Age			
Mean (SD)	39.6 (12.9)	40.0 (13.0)	36.4 (11.9)
Range	19–80	19–80	21–63
Number of treat. sessions			
Mean (SD)	1.59 (0.98)	1.60 (0.99)	1.53 (0.94)
Range	1–5	1–5	1–4
Follow-up from most recent Tx [months]			
Mean (SD)	23.8 (14.8)	26.9 (13.1)	2.31 (1.59)
Range	0.33–60.8	6.43–60.8	0.33–5.70

3.2 Treatment regimen

The patients who completed their therapy (Table 1) received from one to five treatments, with majority of them (74 patients, 64%) receiving only one treatment.

81.9% of the patients (n = 95) showed complete clearance of the lesions, without recurrence observed to date of analysis. Complete clearance was achieved after an average of 1.33 (95% CI, 1.17–1.48) treatment sessions; 21 patients in this group (22.1%) required multiple treatment sessions due to an extensive area affected by warts.

Recurrence was reported by 21 patients, which corresponds to cumulative risk of subsequent EGW of 18.1% (95% CI, 11.1–25.1). There have been 36 recurrence episodes of EGW recorded in 21 patients. The median time to recurrence of the EGW was 1.9 months (IQR = 4.6). In majority of patients with recurrence (n = 15), the warts recurred in a period between 1 and 6 months.

The patients were grouped into six groups according to their age (Table 2). One-way ANOVA with post-hoc Bonferroni correction for multiple comparisons was conducted to determine if patients of different age groups required different numbers of treatment sessions to achieve complete clearance. There was a heterogeneity of variance, as assessed by Levene's test of homogeneity (p = 0.006). Data is presented in Table 2. The results reveal that the differences between age groups are not statistically significant $F(5, 110) = 1.182$, $p = 0.323$.

The chi-square test of homogeneity revealed no statistically significant difference in the frequency of patients with recurrence between the determined age groups, nor was there any statistical difference between the groups regarding the percentage of patients requiring only one treatment.

The observed adverse events of the laser treatment were in some cases mild itching, mild bleeding and mild swelling.

4 Discussion

Public health policy in Slovenia enables routine HPV immunization of all girls at the age of 12 years since 2009, and according to the NIJZ (Slovenia National Institute of Public Health) report, 49.8% of 12-year-old girls were vaccinated in the year 2017. According to an Australian overview of the epidemiological effects of the HPV vaccination, it has not only

Table 2: Effectiveness (Complete Clearance (CC)) of Er:YAG laser treatment within the age groups.

Age group	No. of patients [n]	Mean no. of treatments (95% CI)		Patients requiring single treatment [n, (%)]	Effectiveness of treatment CC [n, (%; 95% CI)]		Mean no. of treatments needed for CC[b] (95% CI)	
19–29	26	1.96	(1.43–2.49)	14 (54.8)	21	(80.7; 73.6–87.9)	1.62	(1.11–2.13)
30–39	35	1.63	(1.26–1.99)	24 (68.6)	27	(77.1; 79.5–84.8)	1.19	(0.94–1.43)
40–49	31	1.45	(1.15–1.75)	21 (67.7)	29	(93.5; 89.1–98.0)	1.34	(1.09–1.60)
50–59	12	1.25	(0.96–1.54)	9 (75.0)	10	(83.3; 76.6–90.1)	1.10	(0.87–1.33)
60–69	8	1.50	(1.05–1.95)	4 (50.0)	4	(50.0; 40.9–59.1)	1.00	(1.00–1.00)
70–80	4	1.50	(0.58–2.42)	2 (50.0)	4	(100; 100–100)	1.50	(0.58–2.42)
Overall	**116**	**1.60**	**(1.42–1.78)**	**74 (63.8)**	**95**	**81.9; 74.9–88.9)**	**1.33**	**(1.17–1.48)**

been shown to have greatly reduced the incidence of cervical cancer but also the incidence of genital warts in the female and male population (15). Nevertheless, the number of patients that are burdened by this stigmatizing disease remains high. The treatment choice for EGW removal is typically decided after discussion between the clinician and the patient, and is usually based on the risk/benefit ratio, accessibility of the treatment, and should also take into consideration the patient's immunologic status (7).

Data on ablative laser techniques used for the treatment of EGW have been mostly limited to CO_2 laser, which has been shown to be very effective in achieving complete clearance at the end of the treatment (7). Laser therapy is significantly more effective than imiquimod 5% cream, trichloroacetic acid (TCA), cryotherapy and combinations of those treatments (7). Ablative Er:YAG laser has been successfully used for treatment of common warts (10,12,16-18) and some studies have shown that Er:YAG laser can be used for the treatment of EGW (11), but systematically collected published data is scarce.

The retrospective analysis of clinical cases from our practice has shown that ablative Er:YAG laser vaporisation is an effective and safe solution for removal of EGW. To our knowledge, the present study represents the largest series of patients with EGW that were treated with ablative Er:YAG laser. The effectiveness of the treatment (no recurrence of lesions) was 81.9%, demonstrating comparable effectiveness of the Er:YAG laser procedure to other available methods.

An 89–95% clearance rate was reported for CO_2 laser (19,20), which was about two times more effective than cryotherapy (20) and comparable to potassium hydroxide (KOH) (19). The observed cumulative recurrence rate of 18.1% (95% CI, 11.1–25.1) is comparable or even lower than that observed with cryotherapy (reported to have up to a 39% recurrence rate (20,21)), nitric-zinc complex (NZC, 29% recurrence rate) (22), and 48.5% for any "complete full destructive" medical intervention (3). Further analysis of our results reveals that in only 12.9% of patients the EGW episode recurred within a period of one to six months, whereas in the remaining 5.2% of patients the EGW recurred in a period longer that six months, which could be considered as a new infection (4), but due to the lack of HPV genotyping in our patients, the nature of the recurrence could not be determined.

Compared to cryotherapy, the Er:YAG laser treatment requires lower number of treatment sessions to achieve full clinical clearance, and can be, as the CO_2 laser procedure (20), basically considered a single-session treatment option. The mean number of required treatments in our study was 1.33, which is markedly lower than the mean number of six to nine sessions reported for cryotherapy (21).

Important factors determining the effectiveness of treatment are the extent and number of lesions, since they may be indicative of an extent of the lesion and its multi-point infection. Some parts of such an infection may be in a latent or subclinical phase and may cause recurrence at a later time (23). Failing to treat these latent and subclinical infections can lead to treatment failure and occurrence of lesions in untreated areas can be misinterpreted as recurrence (23). Cryotherapy is considered as the first-line provider-administered therapy for multifocal small warts (24), but treatment of wider areas may not be well tolerated due to pain and side effects of the treatment, such as local tissue destruction with blistering, ulceration, infection, and loss of pigmentation (20). The possibility of treatment of larger subclinical lesions in the surrounding skin is one of the main advantages of laser vaporisation over cryotherapy. Nevertheless, some patients included in our study still needed multiple treatment sessions in order to avoid extensive tissue ablation and associated discomfort and possible complications.

Age has been recognized as one of the risk factors for infection with HPV, development of EGW, and for effectiveness of EGW treatment; however, our results have shown no statistical difference between different age groups regarding the effectiveness of treatment.

When compared to other modalities, such as KOH (19), CO_2 laser (19) or cryotherapy (20), the ablative Er:YAG laser treatment appears to be associated with lower incidence and milder adverse effects.

The main limitation of our retrospective study is the lack of HPV genotyping; the lack of information about patients' comorbidities that may have influence on the effectiveness of laser treatment; and the relatively low number of patients in higher age groups.

Despite these limitations, our study provides long-term epidemiological information on the frequency of EGW recurrence when treated with ablative Er:YAG laser.

Considering its non-systemic effect and generally mild side effects, Er:YAG laser therapy could be considered the treatment of choice for immunosuppressed patients with extensive lesions, who are unresponsive to TCA or cryotherapy. It can be considered a single-session therapy and has been proven to be particularly suitable for EGW of a large volume or those that are located in anatomical sites that are difficult to access by other ablative techniques.

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