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RESEARCH ARTICLE

Comparative Efficacy of Ultrasonic Scalpel Surgery With Photodynamic Therapy Versus Trichloroacetic Acid Application in Treating HPV-Related Condyloma Acuminata: A Randomized Clinical Trial

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Keywords: condyloma acuminata | photodynamic therapy | trichloroacetic acid | ultrasonic scalpel

ABSTRACT

Human papillomavirus (HPV) infections rank as the most prevalent sexually transmitted infections globally. The Brazilian Ministry of Health recommends the topical use of 70%–90% trichloroacetic acid (TAA) for treating condyloma acuminata, yet this method suffers from a high recurrence rate of 36% and requires roughly six applications. Topical photodynamic therapy (PDT) has shown effectiveness in targeting subclinical lesions, but it also necessitates multiple sessions for complete lesion clearance. This randomized clinical trial evaluates the efficacy of 80% TAA monotherapy against a combined approach of ultrasonic scalpel excision followed by a single PDT session (US + PDT). The US + PDT group required fewer treatment sessions, exhibited superior cosmetic outcomes, and reported zero lesion recurrence during an 18-month follow-up, in contrast to the TAA group's recurrence rate of 33.3%. Notwithstanding, patient-reported pain during PDT application emerged as a significant barrier, affecting treatment adherence and completion rates. Innovating new PDT protocols could potentially address this challenge, enhancing patient compliance and therapeutic success.

1 | Introduction

Genital infections caused by the human papillomavirus (HPV) affect a large fraction of the world's population, estimated at up to 75% of the sexually active population [1]. Dunne et al. showed that the highest incidence of infection occurred among women aged 20–24 [1]. There is a relationship between the type of HPV and the infected tissue, with the mucosa being the most affected tissue, and [2] subtypes 6 and 11 are commonly associated with condyloma acuminata (or anogenital warts), preferably involving regions such as the vulva, perineum, and perianal area [2, 3]. The lesions can be single, but are usually multiple, between 5 and 15, with a thickness between 1 and 10 mm, composed of well-keratinized plaques or papules, making topical treatments difficult and generally compromising local aesthetics after surgical removals, affecting the patient's self-esteem and sexuality [3, 4].

Although several treatments can be used, currently no single treatment is considered effective, as the focus remains on treating the lesions rather than directly targeting the virus. Recurrences are common and are often linked to the patient's immune system [5].

The recommendation of the Brazilian Ministry of Health for condyloma acuminata treatment is the topical application of trichloroacetic acid (TAA) in a concentration of 70%–90%. TAA is a caustic agent that destroys lesions by chemical coagulation of proteins and viral DNA [6]. However, it has a high potential for recurrence, reaching rates of 36% after six applications [7]. Furthermore, it can cause damage to the tissue close to the lesion and, as it has low viscosity, can spread throughout the tissue when applied in excess.

Photodynamic therapy (PDT) is a treatment based on the interaction of a photosensitizer (PS), light with an appropriate wavelength to excite this PS and molecular oxygen species, that promotes cell death [8]. A randomized study carried out by Buzza et al. compared the topical application treatments of TAA 80% and topical PDT using methyl aminolevulinate (MAL) 20%. The recurrence rate observed in the TAA group was 33%, while there were no recurrences in the PDT group, probably due to the selectivity of the technique and ability to treat preclinical lesions. Despite the best treatment results for PDT, both techniques required several sessions, which can overload the healthcare system and lead to dropout of patients [9, 10]. Therefore, ablative treatments combined with PDT can be effective strategies for eliminating the lesions, reducing the number of sessions required for complete treatment, through the initial removal of keratinized tissue, at the same time that it can prevent recurrences [9, 10].

The ultrasonic scalpel (US) has been proven to be safe and has been commercialized in recent decades. It has been used in surgeries such as laparoscopic, mastectomy, and head and neck, promoting vessel sealing and reducing surgical time and the number of postoperative complications [11–13].

This randomized controlled study was performed for the treatment of 36 patients with genital warts caused by HPV, comparing the topical application of TAA 80% and the combined treatment of removing the lesions using a US followed by PDT (US + PDT).

2 | Methodology

This study was carried out at the Lower Genital Tract Pathology Outpatient Clinic of the University Hospital at the Federal University of São Carlos from November 2021 to December 2023 after approval by the Research Ethics Committee (CAAE: 26134319.9.0000.5414, approved on 06/25/2021) and registering in the Universal Trial Number (UTN: U1111-1305-3128, on 03/22/2024).

This is a randomized and controlled clinical trial for treatment of female patients between 18 and 60 years old with a diagnosis of genital condylomatosis confirmed by clinical and, if necessary, histopathological examination. Patients who were pregnant, lactating, immunologically suppressed (HIV carriers, transplanted individuals, or undergoing chemotherapy), and people who were allergic to any component used (cream or anesthetic) were excluded from the study, as well as those who had undergone other treatments for HPV lesions in the last 12 months. The maximum lesion number for the study was not established. The study included 36 patients, half of whom were treated with PDT + US and the other half with the standard treatment, TAA 80%.

The intent-to-treat (ITT) was calculated using the following equation: $n = \frac{2[(a+b)^2\sigma^2]}{(\mu_1-\mu_2)^2}$. Let n be the sample size in each group, μ_1 the population mean of the treatment for Group 1, μ_2 the population mean of the treatment for Group 2, $\mu_1 - \mu_2$ the difference in means, σ^2 the population variance, a the conventional multiplier when α is 0.05, and b the conventional multiplier when power β is 0.80. In this context, considering $a = 0.05$ and $b = 0.20$, we have the respective values of 1.96 and 0.84 in the z-table of the standard normal distribution. Considering a difference in means of 20 and a standard deviation of 20, we have a total sample size of $n = 36$ patients, 18 in each arm of treatment.

The allocation of patients was carried out according to a randomization table previously created by the researchers in Excel Software, randomizing the sequence of two groups based on the number of patients treated.

2.1 | Treatment With US + PDT Combination

To excise the lesions, the skin was first sterilized with 1% aqueous chlorhexidine gluconate. This was followed by administering a local anesthetic using 2 mL of 2% xylocaine without a vasoconstrictor, delivered through a 5-mL syringe with a 13 × 0.45 mm disposable needle. Subsequently, the lesions were excised using ultrasound guidance, and an occlusive dressing was applied for 24 h post-procedure. Patients were advised to take a standard analgesic should they experience any discomfort.

The healing of the first three patients in the US + PDT group was monitored after the lesions were excised to determine the interval between procedures; these patients returned weekly.

After 21 days of excision, patients were instructed to apply MAL 20% (PDTPharma, Cravinhos, Brazil) at home, 3 h before the scheduled time at the outpatient clinic. The patients applied the cream to the regions where the lesions were removed and used PVC film over the area to avoid loss of the medication and to ensure absorption of the cream by the skin tissue. After this period, the lesions were illuminated with the CerCa 150 system (MMOptics, São Carlos, Brazil) based on LEDs emitting at 630 nm. The procedure involved an irradiance level of 80 mW/cm² over a duration of 21 min, resulting in a total energy delivery of 100 J/cm² [9, 14]. During irradiation, patients were asked every 3 min regarding their pain score, with 0 being the total absence of pain and 10 being the maximum level of pain endured by the patient.

2.2 | US Characteristics

The US used was a prototype developed in partnership between the Sao Carlos Physics Institute, Brazil (IFSC) and the company

WEM (Ribeirao Preto, Brazil), which allowed the cutting and coagulation of soft tissues with broad bleeding control, without causing peripheral thermal injuries. This system does not use electrical current through the patient, other devices (such as magnets), and earth return electrode (patient plate), which makes it possible to use it in patients with a pacemaker. The system operates between 40 and 60 kHz with power ranging from 0 to 0.1 W, for better cutting effects in soft tissues.

2.3 | Topical Treatment Using TAA 80%

The application was carried out punctually in each region that contained a visible lesion using a cotton swab. Several seconds after applying the acid, it was possible to observe a whitish color that formed in the region. Next, liquid petroleum jelly was applied to the entire surrounding area to prevent the acid from dripping and damaging healthy skin. The patient was instructed to wash the area with soap and water 6 h after the procedure. Patients treated with topical TAA often report pain during application (for a few minutes), but not after the use. Therefore, the use of analgesics was not recommended for these patients.

These patients returned weekly until the lesions completely disappeared or until the limit of 10 sessions was reached. Patients who did not receive complete treatment in these 10 applications were referred for surgical treatment.

2.4 | Patients' Follow-Up

The patients had follow-ups for 1, 3, 6, 12, and 18 months after completing treatments. At each return visit, photographic images of the lesion areas were recorded and clinically assessed for recurrence. The appearance of any genital condyloma lesion in the follow-up was considered a recurrence, the patient was referred for surgery, and this new treatment was not included in the study. Although aesthetic results have not been reported as a problem in patients treated with topical TAA [4], in this trial the treatment with US + PDT was evaluated to see if its outcome would be inferior. Photographic images of the lesions after 30 days of treatment were presented to a plastic surgeon who blindly evaluated the aesthetic aspect.

2.5 | Statistic Evaluation

Differences in patient characteristics between groups were assessed using Student's *t*-test. To compare the aesthetic results of the two groups, we applied a blind test to the plastic surgeon for the tissue evaluation, without knowing the patients and the treatment groups. The evaluation of scars was done by analyzing various properties of the skin. For classification, the method proposed by Yeong et al. was used to evaluate characteristics such as the surface, margin, scar thickness, and pigmentation of the tissues treated [15]. The recurrence was evaluated using the disease-free recurrence function estimated by the Kaplan–Meier function, which is the probability of an event (in this study, recurrence) not occurring until a certain time point. The curve starts at 1 (i.e., disease-free recurrence probability equal to 1 at the beginning of the study) and may decrease as time passes and the events of interest occur.

3 | Results

In total, 36 patients with condyloma acuminata in genital regions were included in the study. In each protocol, 18 patients were randomly allocated. The study flowchart is presented in Figure 1.

Table 1 presents the patients' characteristics according to the treatment group.

TABLE 1 | Patients' characteristics. The statistical *t*-test was applied to the age values, while the Mann–Whitney test was applied to the values of body mass index, number of pregnancies, and sexual intercourse.

	TAA	US + PDT	*p* value
Age (years)	42	39	0.5331
Body mass index	28.54	26.50	0.3588
Number of pregnancies	1	1	0.5963
Age of sexual intercourse initiation (years)	19	17	0.5775

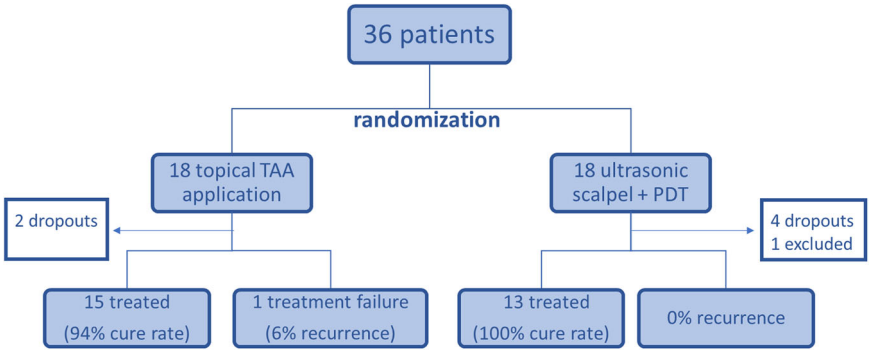

FIGURE 1 | Flowchart of the patients' stay in each protocol.

All patients treated by the US + PDT protocol successfully eliminated their lesions. On the other hand, the group treated with TAA had a cure rate of 94%, with therapeutic failure being observed in one patient who presented persistent lesions after 10 treatment sessions.

Among the patients in the US + PDT group, there was even one patient with refractory lesions for more than 2 years of previous topical treatments with TAA, imiquimod, and PDT. In the US + PDT protocol proposed in this study, the lesions were completely eliminated, with no recurrences after an 18-month follow-up.

However, the US + PDT had a greater number of dropouts compared to the TAA. Of the dropouts, the main complaint was the pain felt during PDT and the remaining patients did not return to contact. One of the patients became pregnant between treatment sessions and had to be excluded from the study.

For the group treated with topical application of TAA, in Figure 2 it is possible to observe the evolution of a patient's condyloma during treatment. Figure 2A shows the initial condyloma when the patient was recruited to the study; Figure 2B shows the condyloma after topical application of the acid in which the white color that forms in the tissue due to the procedure is evident; Figure2C shows the region after four treatment sessions with the absence of condyloma but the presence of hypopigmentation; and Figure 2D shows the region 1 month after the treatment—the tissue reveals that this change in pigmentation prevails.

In the other group, US + PDT treatment, the healing monitoring of the first three patients was used to determine the interval time between procedures. These patients returned to the outpatient weekly until complete tissue healing and clinical absence of inflammation were observed. The image record of one of the patients is shown in Figure 3. From Figure 3B it is possible to observe, after resection, the absence of bleeding, as the instrument allows cutting and cauterization of the tissue simultaneously. Two weeks after resection (Figure 3C), the tissue is not yet completely healed and presents inflammatory characteristics, such as redness and swelling. Already 3 weeks after the procedure (Figure 3D), it is possible to notice that the tissue is healed and without visual aspects of inflammation, with an interval of 3 weeks between procedures being determined.

After determining the best interval between procedures, the next patients were treated using a 3-week wait for tissue healing and PDT. The evolution of a patient throughout the treatment after removal of the lesion with a scalpel followed by PDT is shown in Figure 4. In Figure 4A, it is possible to observe a condyloma on the vulva at the time the patient was included in the study; Figure 4B shows the region after excision using a US without bleeding, and Figure 4C shows the region after 4 weeks of excision. At the time of PDT return, scarred tissue and the presence of hyperkeratinization can be seen, and, in Figure 4D, 3 months after PDT, it can be seen to be completely regenerated, with no scar marks and with excellent cosmetic results.

In this study, 4 of the 18 patients included in treatment with US + PDT withdrew from treatment due to pain experienced

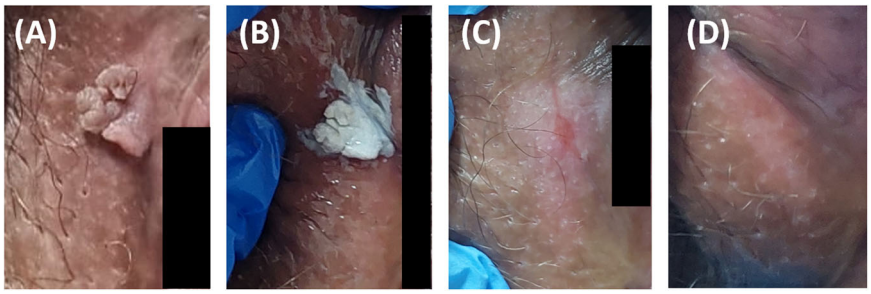

FIGURE 2 | Patient LZM, 44 years old, with a single lesion of condyloma on the vulva (A) initially, (B) immediately after an application of 80% TAA, (C) with clinical absence of lesion after four treatment sessions, and (D) 1 month after completion of treatment.

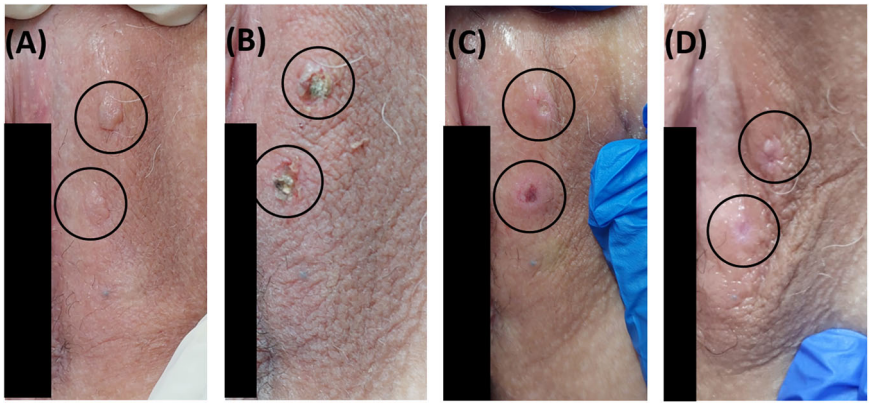

FIGURE 3 | Patient IPG, 33 years old, with condylomas in the vulva region (A) initially, (B) immediately after removal with an ultrasonic scalpel, and after (C) 2 weeks and (D) 3 weeks.

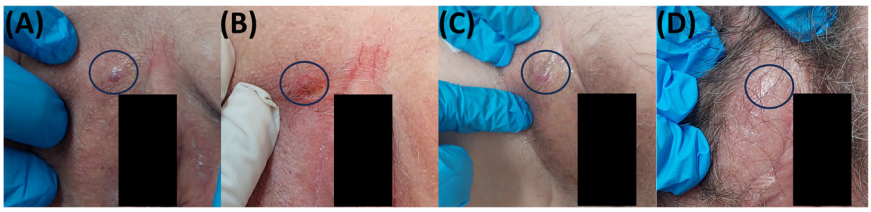

FIGURE 4 | Patient MFLG, 60 years old, with condylomas in the vulva region (A) initially, (B) immediately after removal with an ultrasonic scalpel, (C) after 3 weeks on return to PDT, and (D) 3 months after completion of treatment.

during PDT. The patients in this study were asked about their pain score every 3 min of the 21 min of irradiation, with scores between 0 and 10, with 0 being the total absence of pain and 10 being the most intense pain felt by the patient. Severe (between 7 and 10), moderate (between 4 and 6.9), and mild (between 0 and 3.9) pain classifications were used for the scores given by patients, and each classification is presented by the percentage of patients throughout the treatment period in Figure 5.

In Figure 5, it is possible to observe that the percentage of patients with severe pain decreases over the irradiation time, while the percentage of patients with mild pain increases being the patients' majority (around 64%) at PDT end.

The average number of sessions performed in patients who completed the treatments was calculated. The average and median number of sessions performed in the treatment groups are shown in Table 2, along with the minimum and maximum number of sessions per treatment. Using the Mann–Whitney test, it was found that the US + PDT treatment group had a significantly lower average number of sessions compared to the TAA group.

Of the 14 patients who completed the treatment in the US + PDT group, eight completed the treatment in just two sessions. Two patients had numerous lesions, requiring the treatment to be divided into three stages, each consisting of two sessions (one for lesions excision and one for the PDT application, totaling six sessions). This division was necessary due to the time required for local anesthesia to take effect. Additionally, four patients developed new lesions before returning for PDT, necessitating new excisions before the PDT session for the newly treated areas.

After completing the treatments, the patients had follow-up for 1, 3, 6, 12, and 18 months for clinical evaluation of possible lesion recurrence. The evaluation of this follow-up was carried out using Kaplan–Meier and is shown in Figure 6. Note that at the beginning of the study, both groups (US + PDT and TAA) have a disease-free recurrence of 1. At the first follow-up, that is, the first month, the disease-free recurrence l of the TAA group decreases to 0.882 as two patients experienced recurrence under this treatment. Subsequently, at the 1-year follow-up, another patient experienced recurrence, leading to a further decline in the disease-free recurrence curve for the TAA group to 0.667 at the time point of 18 months.

The patients' 30-day follow-up photos were sent to a plastic surgeon who analyzed the images about the surface, margin,

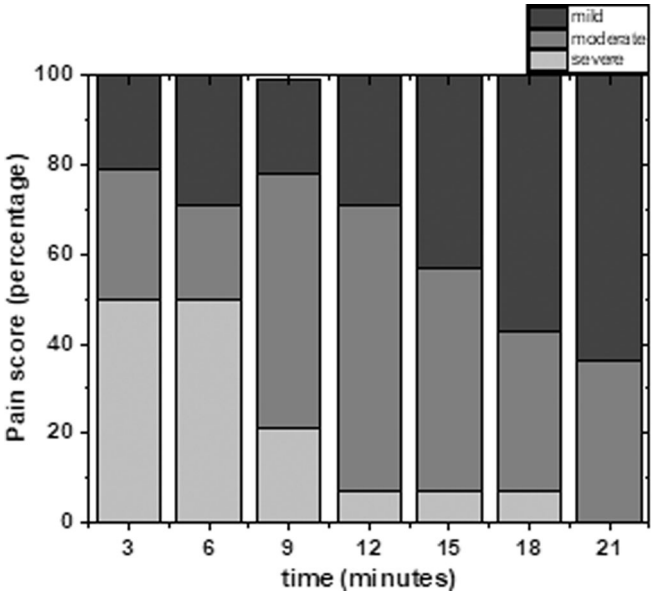

FIGURE 5 | Pain score classifications during PDT application in the percentage of patients.

scar thickness, and pigmentation of the treated tissues, without him knowing each patient's treatment group. In Table 3, we can see the percentage of patients classified according to each characteristic, and the highlighted lines show the best results evaluated by the doctor, that is, normal appearance after healing. The group treated with US + PDT, in all analyzed criteria, had more patients classified as having normal tissue appearance compared to patients in the TAA group.

4 | Discussion

When performing PDT, the aim is to obtain a selective treatment, in which FS molecules accumulate preferentially in differentiated cells (infected by the HPV). In inflamed and healing tissue, other factors can influence cellular metabolism, causing accumulation of PpIX in regions that are also not of interest for treatment, affecting selectivity [9, 16]. The interval between US and PDT was defined by monitoring tissue healing after the excision of the lesions with the US, with the aim of obtaining a more selective treatment.

Pain sensation during topical PDT is commonly reported in clinical studies and is considered a limitation of treatment [17]. However, some studies indicate that this pain is subjective and

TABLE 2 | Mean and median number of sessions in the treatment groups.

	Mean	Median	Minimum	Maximum
TAA	4.47	4	1	12
US + PDT	3.00	2	2	6

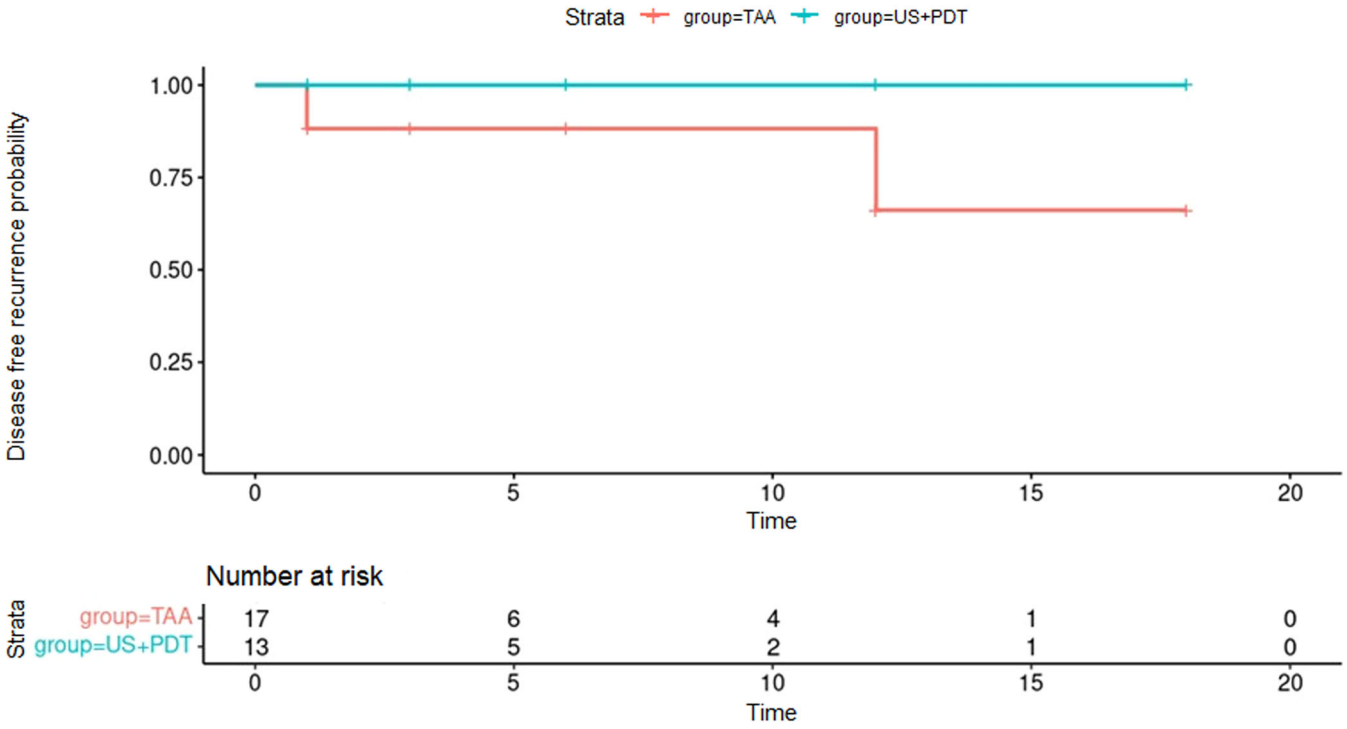

FIGURE 6 | Kaplan–Meier curve of patient follow-up.

TABLE 3 | Characteristics of patient healing according to the treated group.

		TAA (%)	US + PDT (%)
Surface	Uneven	50.0	33.3
	Normal	16.7	66.7
	Flat	33.3	0
Margin	Elevated	50.0	41.7
	Normal	50.0	58.3
Scar	Thick	58.3	41.7
	Normal	41.7	58.3
Pigmentation	Hypo	58.3	41.7
	Normal	33.3	41.7
	Hyper	8.4	16.6

can vary greatly for each patient, influenced by factors such as gender, age, and emotional aspects [18]. Reactive oxygen species, transient receptor potential channels, and inflammatory responses are also possible mechanisms responsible for the pain felt during treatment [19, 20]. In the first minutes of treatment, there is a greater photodynamic action due to the higher PS concentration present in the tissue. As the treatment is carried out and these molecules are consumed, the concentration of available PS decreases and fewer reactions occur that induce the pain [21]. Therefore, it is common for this sensation of pain to decrease throughout the treatment, as also demonstrated in this study. Furthermore, the number and region of the lesions treated can also affect this pain sensitivity. Lesions in the mucosal areas, for example, such as the clitoris and introitus, tend to present greater sensitivity to pain when compared to skin lesion treatments, such as the vulva's external part and perianal region [20, 22].

In this study, disease-free recurrence of patients after treatments was evaluated. The disease-free recurrence of patients exposed to treatment with AAT was shown to be lower compared with the disease-free recurrence of patients exposed to treatment with US + PDT throughout the follow-up period. Considering that the use of US would present an efficacy very close to that of conventional surgical removal of localized lesions, it is only possible to remove visible lesions and not treat subclinical lesions. There is extensive literature on local treatment, which considers this efficacy to be around 74% and an average recurrence time of 11 weeks for the treated lesions. In this study, we used the US + PDT treatment in combination [23]. With the application of PDT, the aim is to achieve selective treatment by preferentially accumulating PpIX in differentiated cells, in this case, cells infected by the HPV, even reaching contaminated tissue portions that have not yet developed visible

lesions (subclinical lesions). This selectivity, added to the technique's ability to stimulate an increase in the immune system, may have favored the absence of recurrences observed in this treatment group, compared to the recurrence rate which reached approximately 0.33 observed in the TAA group over the 18 months of follow-up [11].

Treatment using US + PDT showed promise in the treatment of genital condylomas, reducing the chances of recurrence and the number of sessions needed for treatment compared to other topical treatments such as the application of TAA 80% and benefiting the patient and the outpatient dynamics, in addition to providing superior cosmetic results. Topical treatments such as the application of TAA can often require several sessions to eliminate condylomas, overloading the outpatient clinics providing care for these patients and causing discomfort for them [4, 24]. However, some perspectives must be achieved, such as improvement of protocol and establishment of management strategies to reduce patient pain.

After surgical procedures to remove condylomas using the US, the tissue goes through a process of regeneration and healing, which can suppress the local immune system, facilitating the growth of subclinical lesions of contaminated tissue [25]. One of the limitations observed in this protocol was the appearance of new lesions in the interval between procedures. As a future perspective, we intend to establish a new protocol with PDT being performed immediately after the excision of condylomas with the largest sample number of patients [9, 26]. Furthermore, in surgical removals using the US, no bleeding or charring of tissue was observed, which would mean a physical barrier to the penetration of both the cream and light that can compromise the effectiveness of PDT.

5 | Conclusions

This randomized study facilitated a direct comparison between the Brazilian health system's recommended treatment (topical application of TAA 80%) and the innovative US + PDT combination therapy. The latter demonstrated a reduction in recurrence rates and required fewer treatment sessions. This efficiency translates to decreased clinical workload, optimized outpatient services, and yielded cost savings. Moreover, it can alleviate the psychological burden on patients by minimizing feelings of embarrassment.

Additionally, the US + PDT therapy outperformed in all evaluated aesthetic parameters, substantially enhancing the patient's quality of life, self-image, and confidence. Despite the challenge of procedural discomfort, the combined treatment shows promise. It is imperative that we develop new protocols to refine this promising treatment, aiming to maximize therapeutic efficacy while minimizing patient discomfort.

Author Contributions

Study conception and design: Valter Fausto dos Santos, Ian Carlos de Barros, Vera Lucia Damasceno Tomazella, Adriane Caroline Teixeira Portela, Semira Silva de Arruda, Hilde Harb Buzza, Natalia Mayumi Inada, Vanderlei Salvador Bagnato, and Mirian Denise Stringasci. Data collection: Valter Fausto dos Santos, Ian Carlos de Barros, and Mirian Denise Stringasci. Analysis and interpretation of results: Valter Fausto dos Santos, Ian Carlos de Barros, Vera Lucia Damasceno Tomazella, Adriane Caroline Teixeira Portela, Semira Silva de Arruda, Hilde Harb Buzza, Natalia Mayumi Inada, Vanderlei Salvador Bagnato, and Mirian Denise Stringasci. Draft manuscript preparation: Valter Fausto dos Santos, Ian Carlos de Barros, Hilde Harb Buzza, Natalia Mayumi Inada, Vanderlei Salvador Bagnato, and Mirian Denise Stringasci. Reviewed the results and approved the final version of the manuscript: Valter Fausto dos Santos, Ian Carlos de Barros, Vera Lucia Damasceno Tomazella, Adriane Caroline Teixeira Portela, Semira Silva de Arruda, Hilde Harb Buzza, Natalia Mayumi Inada, Vanderlei Salvador Bagnato, and Mirian Denise Stringasci.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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