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Paring and Intense Pulsed Light Versus Paring Alone for Recalcitrant Hand and Foot Warts: A Randomized Clinical Trial With Blinded Outcome Evaluation

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Background and Objectives: Treatment of recalcitrant viral warts remains a therapeutic challenge. Intense pulsed light (IPL) has been suggested effective to clear wart tissue. The objective was in a randomized controlled trial to assess the efficacy of paring followed by IPL versus paring alone for recalcitrant hand and foot warts.

Materials and Methods: Eighty-nine patients with recalcitrant hand and foot warts were included and randomized (1:1) to three treatments at 3-week intervals with either paring of warts followed by IPL or paring of warts alone. IPL was given with the Ellipse Flex IPL system (Danish Dermatologic Development A/S, Hørsholm, Denmark, 400–950 nm, 5.5 millisecond pulse duration in double pulses with a 2 millisecond interval, 26.0–32.5 J/cm^2 repetitive passes). The primary outcome was complete and partial clearance of warts evaluated by blinded photo assessment at 6 weeks after final treatment. Secondary outcomes were treatment related pain and adverse reactions.

Results: We found no significant difference in clearance of warts between the two intervention groups (OR 1.64, 95% confidence interval 0.62–4.38). Paring followed by IPL resulted in complete or partial clearance of wart tissue in nine (22%) and five patients (12.2%) versus five (13.5%) and four patients (10.8%) from paring alone. Mostly plantar warts were treated (92.1%). The pain intensity after paring and IPL was moderate and significantly higher than the pain intensity after paring alone ($P<0.0005$). No adverse reactions were observed from the two interventions.

Conclusion: Paring followed by IPL did not differ significantly from paring alone in clearance of recalcitrant hand and foot warts but caused significantly more pain. Lasers Surg. Med. 42:179–184, 2010. © 2009 Wiley-Liss, Inc.

Key words: adverse reactions; intense pulsed light; pain; paring; viral warts

INTRODUCTION

Cutaneous viral warts are benign epithelial neoplasms, caused by infection with different types of human papilloma virus (HPV). The prevalence of HPV infection is estimated at 3.5% among adults and occur even more frequently among children [1,2]. The most common site of infection is the hands and feet with a predilection for hyperkeratotic tissue. Spontaneous resolution is observed in approximately two-thirds of warts within a 2-year period but warts may cause social, cosmetic, and functional problems as well as the lesions may be painful [3]. First line treatments, which combine paring of warts with keratolytic topical agents and cryotherapy, may cure up to 73% of simple warts within a 3-month period [4]. However, some warts are recalcitrant and persist for many years in spite of several treatment approaches like cantharidin, topical or systemic immunotherapy, intralesional bleomycin, CO_2-laser, photodynamic therapy and surgery. Accordingly, recalcitrant warts represent a therapeutic challenge among patients at outpatient dermatologic clinics.

Newer, non-destructive interventions such as the pulsed dye laser (PDL) and intense pulsed light (IPL) have been suggested for treatment of recalcitrant warts [5–15]. The mechanism of action is assumed to be selective destruction of superficially papillary capillaries of the wart as well as thermal injury of the heat-sensitive HPV [5]. IPL has become increasingly popular during the last decade and is currently used in the treatment of recalcitrant warts in secondary care units and dermatological hospital departments. Nevertheless, the evidence supporting IPL and lasers in the treatment of warts is very limited. No randomized trials have assessed the effect of IPL in the treatment of warts and the effect from PDL was in one randomized trial similar to conventional keratolytic

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treatment with no significant difference in the clearance of warts [16].

The purpose of this randomized trial was to assess the efficacy and adverse events for paring plus IPL versus paring alone for recalcitrant hand and foot warts in a randomized trial with blinded outcome evaluation.

PARTICIPANTS AND METHODS

Patients

Consecutive patients with recalcitrant hand and/or foot warts were included in the trial during April 2006 to January 2008. Patients were referred to the outpatient Departments of Dermatology at Bispebjerg University Hospital, Århus University Hospital, and Viborg Hospital, Denmark. Recalcitrancy was defined as the persistence of warts for at least 2 years and no efficacy of previous keratolytic treatments with salicylic acid and/or lactic acid for more than 3 months. Exclusion criteria were age below 18 years, lack of informed consent, immunosuppressive therapy, pregnancy or breast-feeding, previous IPL-treatment for viral warts, known photosensitivity, tendency to produce keloids or hypertrophic scars, mosaic or plane warts, or lack of ability to follow the treatment protocol. The protocol was registered at ClinicalTrials.gov (NCT00254280), approved by The Committee on Biomedical Research Ethics of Copenhagen and Frederiksberg (KF 01 255566) and the Danish Data Protection Agency (2004-41-4762).

Randomization

When an eligible patient accepted to participate in the trial, a clinical assessment was performed where all hand and foot warts were counted and registered. The extremity with the highest number of warts was selected for inclusion and randomized (1:1) to three treatments at 3-week intervals with either paring of warts followed by IPL (experimental intervention) or paring of warts (conventional intervention). All the patient's warts received the same treatment as the allocated intervention, but only warts on the selected extremity was evaluated. Central treatment allocation was carried out blindly by an independent telephone randomization system (Copenhagen Trial Unit) that was based on a computer-generated randomization list. The allocation was concealed until immediately before an included patient was to receive the first treatment. Randomization was stratified by center, and hand or foot warts to ensure an equal balance of patient characteristics within each intervention group.

Interventions

A trained nurse pared the horny layer of all warts with a scalpel until visualization of blood vessels. The nurse was blinded to which of the two interventions the patient received. IPL were given immediately after the paring procedure with the Ellipse Flex IPL system (Danish Dermatologic Development A/S, Hørsholm, Denmark), which is a second generation IPL system. Dual mode filters restricted the emitted light to a wavelength band from 400 to 950 nm (Tumor applicator, $10 \times 10\,mm^2$ contact probe). Treatments were applied with minimal pressure to wart tissue, utilizing a 5.5 millisecond pulse duration administered in double pulses with a 2 millisecond interval and fluences from 26.0 to $32.5\,J/cm^2$. Pulses were delivered in repetitive passes until a gray discoloration of the wart was achieved, starting with the lowest energy level for the first pass and increasing energy levels in increments of $2\,J/cm^2$ with subsequent passes until a maximum of five passes (26, 28, 30, 32, $32.5\,J/cm^2$). The interval between repetitive passes was a few seconds. Trained dermatologists administered IPL at all treatment sessions (MH, HKL, MC, and HL).

Patients in both intervention groups were not allowed to use other local wart treatments except for a minimum of paring if pain developed due to hyperkeratotic wart tissue.

Assessment of Outcomes

The primary outcome measure was complete and partial clearance of wart tissue on the selected extremity (treatment response) that was statistically evaluated with patients as the unit of analysis. Secondary outcome measures were treatment related pain, adverse reactions and events from the two interventions.

Treatment response and adverse effects were evaluated 6 weeks after the last of three treatments by blinded, photographic evaluations on a semi-quantitative clinical assessment and were compared with pre-treatment photos. One blinded assessor evaluated all photographs (KT). Treatment response was categorized into three groups, depending on the extent of clearance of wart tissue: No response (no change), partial response (reduction of visible wart tissue), and complete response (no visible wart tissue). Photographs were taken with a Canon Digital Camera (EOS 20D, Canon, Nagasaki, Japan) equipped with a lens mounted ring flash (Canon Macro Lens EF-S 60 mm 1:2:8 USM) and standardized in terms of magnification, lightning, and positioning.

Patients assessed the pain intensity before and immediately after the first and third treatments. Pain intensity was assessed using a numeric scale ranging from 0 to 10 ($0 =$ no pain and $10 =$ worst imaginable pain). Adverse reactions such as hyper- and hypopigmentation, atrophic and hypertrophic scarring were recorded at follow-up visits. Moreover, adverse reactions, related to interventions, and adverse events, unrelated to interventions, were recorded throughout the trial.

Statistical Analysis

A sample size calculation with a type-1 error of 5%, a type-2 error of 10%, and an expected cure rate in the control group of 30% and a minimum relevant difference in cure rate of 20% was conducted before the trial was launched. We calculated that a total of 80 patients (40 patients in each intervention-group) was needed.

All data analyses were carried out according to a pre-established analysis plan. Only blinded intention-to-treat analyses were conducted. Descriptive data are presented as medians with range and interquartile range (IQR). An

ordinal logistic regression analysis (deriving the odds ratio, OR) was performed with treatment response at week 6 after the last of three treatments as the dependent variable and intervention as the single covariate with paring as the reference. This analysis was repeated with patient age, sex, total number of warts and number of locations of warts, prior to intervention included as covariates as well. The distribution of pain scores was compared for the two interventions using a non-parametric test (Mann–Whitney) since the distribution were not Gaussian and could not be transformed to Gaussian distribution.

RESULTS

Patients

Figure 1 illustrates the trial flow chart. A total of 106 patients were screened for trial inclusion at three centers of which 89 patients were eligible and randomized to interventions ($n = 45$ patients received paring plus IPL and $n = 44$ patients received paring). Seventy-seven patients were included at Bispebjerg Hospital, eight at Århus Hospital, and four at Århus and Viborg Hospital. The major reason for ineligibility was lack of informed consent ($n = 15$). Two patients randomized to paring plus IPL were lost to follow-up and one patient discontinued due to IPL-related pain. In the paring group, two patients were lost to follow-up, one of whom had received one IPL-treatment by mistake although randomized to only paring. No other patients randomized to paring alone, received IPL. Entry characteristics of patients and warts did not differ importantly between the two groups (Table 1).

Eighty-three patients completed the trial treatments and presented for post-treatment evaluations from April 2006 to July 2008. Clinical photos were missing from five patients, who were excluded from treatment response analysis. In total, data from 78 patients was included in the treatment response intention-to-treat analysis (Fig. 1).

Treatment Effect 6 Weeks After Final Intervention

Both patients receiving paring plus IPL and paring alone experienced complete and partial clearance of warts and we found no significant difference in treatment efficacy between the two intervention groups at 6 weeks post-treatment (OR 1.64, 95% confidence interval 0.62–4.38, $P = 0.32$). A similar distribution of treatment response was observed in the paring plus IPL and paring groups (Table 2). Paring plus IPL resulted in complete and partial clearance of wart tissue in nine (22%) and five (12.2%) patients, whereas five (13.5%) and four (10.8%) patients obtained complete and partial clearance from paring alone. Slightly more patients, 28 of 37 (75.7%) patients, experienced no response to paring compared with 27 of 41 (65.9%) patients who were treated with paring plus IPL, but this difference was not statistically significant.

Covariates such as sex, age, total number of warts prior to intervention, and number of extremities involved were not correlated to treatment response (Table 3).

Since the efficacy of the two interventions seemed similar, we combined the treatment response rates and assessed the relation to the two stratification variables. It was found that center was not related to treatment response ($P = 0.99$), but hand warts tended to respond better to treatment than plantar warts ($P = 0.06$). At-home paring of warts due to painful hyperkeratosis of wart tissue was necessary for seven patients in the paring plus IPL-group and four patients in the paring group. The treatment response was independent of whether at-home paring was performed or not ($P = 0.44$).

Pain Intensity

The intensity of pain experienced after paring plus IPL was significantly higher than the pain intensity after paring alone ($P < 0.0005$). Patients experienced moderate pain of similar intensities after the first and after the third treatment (median 6.0 (range 1.0–10) vs. 5.3 (0.5–10), $P = 0.13$) (Table 4). Pain related to paring alone was at a low and stationary level from the first to the third treatment (median 0 (range 0–5) vs. 0 (0–7)) (Table 4).

Safety Assessment

No patients developed hyper- or hypopigmentation, atrophic or hypertrophic scars and no other adverse events or reactions were reported during the trial.

DISCUSSION

This study is the first randomized clinical trial that evaluates the effect of IPL for recalcitrant hand and foot warts. We used a specific IPL device at specific settings and we found no significant difference in treatment outcomes between patients treated with paring of warts followed by IPL versus paring of warts alone. Patients experienced moderate pain from paring plus IPL and the pain intensity was significantly higher from paring and IPL than from paring alone.

In clinical studies, the efficacy assessment from wart treatments is hampered by a high degree of spontaneous resolution of warts and heterogeneity of patients may account for highly variable cure rates from study to study [4]. High-quality randomized clinical trials are, therefore, important in order to assess the true treatment efficacy, and there is a particular need for randomized clinical trials in the field of light and laser treatments of warts due to lack of existing evidence. In this randomized trial, we used well-defined in- and exclusion criteria to ensure a homogenous study population, as well as we applied centralized treatment allocation, blinded evaluation of treatment outcome and blinded data analysis in order to minimize investigator-associated bias [19–21].

Furthermore, we decided to use the number of patients cured as our primary outcome measure rather than the numbers of warts cured, which was based on the fact that clearance of wart tissue is the desired outcome (end-point) for patients and therefore, a more clinically relevant outcome measure (end-point) [4].

The efficacy of IPL in the treatment of recalcitrant or simple viral warts has not previously been assessed in randomized clinical trials, nor in non-randomized con-

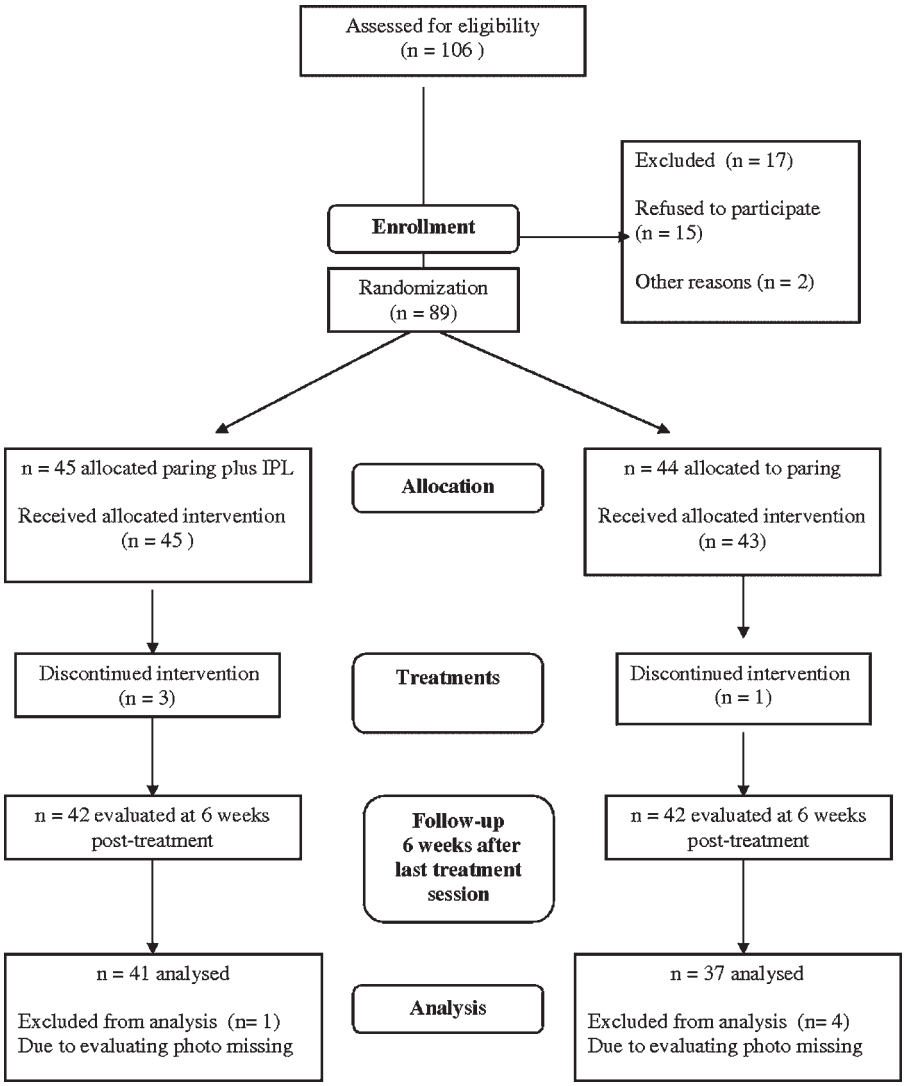

Fig. 1. Trial flow chart.

trolled or uncontrolled studies. IPL is a non-destructive treatment modality using intense pulsed broadband light with the wavelength spectrum being dependent on the cut-off filter used. Presumably the light selectively targets superficial capillaries of the warts, as well as melanin in the dermal–epidermal junction may be a target. In comparison, PDL is monochromatic light of 585 nm that is thought to exhibit a similar non-destructive mechanism of action on

TABLE 1. Distribution of Patient Demographic and Entry Variables Between the Two Intervention Groups and in the Total Patient Group

Quantity	Paring plus IPL ($n = 45$)	Paring ($n = 44$)	Total ($n = 89$)
Females, no. (%)	17 (37.8)	16 (36.4)	33 (37.1)
Age, years, median (IQR)	40.0 (30.5–48.5)	46.0 (32.3–52.0)	42.0 (31.0–52.0)
Total no. warts, median (IQR)	4.0 (1.0–11.0)	3.5 (1.0–6.0)	4.0 (1.0–7.0)
Location at hands, no. (%)	3 (6.7)	4 (9.1)	7 (7.9)
Pain before first treatment, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)

IQR, interquartile range.
Pain score: 0 = no pain and 10 = worst imaginable pain.

TABLE 2. Treatment Response According to Interventions With Paring Followed by IPL Versus Paring Alone

	Evaluations week 6 after last intervention ($n = 78$)		
Intervention	No response	Partial response	Complete response
Paring plus IPL, *n* (%)	27 (65.9)	5 (12.2)	9 (22.0)
Paring alone, *n* (%)	28 (75.7)	4 (10.8)	5 (13.5)
Total, *n* (%)	55 (70.5)	9 (11.5)	14 (17.9)

n, number of patients. No significant differences in treatment response was found between paring plus IPL and paring alone, $P = 0.32$.

wart tissue, although differences in pulse duration between PDL and IPL may influence the treatment outcome.

Only one previous randomized clinical trial by Robson et al. [16] has assessed PDL efficacy for simple warts. This trial involved 40 patients and found no significant difference in cure rates from four treatments at monthly intervals between PDL (66% of warts) and conventional treatment with cryotherapy or cantharidin application (70% of warts), concluding that PDL is as effective as conventional treatment for simple warts [16]. These findings are in accordance with the results of the present trial, as we found no significant difference between paring plus IPL and conventional paring alone. Our results also indicate that IPL did not have an additional effect in itself. This corresponds with the results of one non-randomized, controlled study, which found that PDL plus salicylic acid had similar effect as PDL in the clearance of viral warts (69.7% and 66.6% of warts, respectively) after five treatment sessions at 4-week intervals [14]. Unfortunately, it is not possible to extract data on a patient level from these studies of simple warts. The wart cure rates can, therefore, not be compared with our complete patient clearance rate at 22% of paring plus IPL. Furthermore, we assessed the treatment efficacy on recalcitrant warts in this study, which have an expected lower cure rate than simple warts. Several uncontrolled studies have found PDL able to clear 48–93% of simple and/or recalcitrant warts at various locations, and two studies have reported of low cure rates at 0% and 6.5% of warts [5–13,15,17,18]. Cure rates observed in these non-randomized, non-controlled studies do not account for the spontaneous resolution of warts and the high risk of bias makes interpretation and validity of these outcomes uncertain.

Viral warts are very common and most often resolve spontaneously, but may be recalcitrant to numerous treatments. Treatment modalities should reflect the benign character of HPV infection and be effective with few adverse reactions. In our trial, a slightly higher percentage (22%) of patients obtained complete clearance after paring plus IPL compared with paring alone (13.5%). It may be argued that these results comprise a risk of type-2 error due to a lower treatment response than estimated in the minimum difference in cure rate of 20% from the pre-study sample size calculation. If another trial was conducted, a smaller difference in treatment outcome may be observed in favor of paring plus IPL. However, we consider this aspect as hypothetical as the treatment outcomes are similar and as conventional sample size calculations were followed before study initiation. In the present study, the proportion of plantar warts (92.1%), which seems to be more resistant to treatment, may nevertheless contribute to an overall low cure rate. We performed three treatment sessions at a 3-week interval, which corresponds to previous trials with PDL, and it is unlikely that additional treatment sessions or shorter treatment intervals would have provided higher clearance rates. However, future trials may clarify these questions.

Adverse reactions from PDL for warts are described as crusting and in some studies hypopigmentation and scarring occurred. We found IPL to be safe and no patients

TABLE 3. Treatment Response According to Intervention and Covariates

Analysis	Covariates	Odds ratio (OR)	95% confidence interval of OR	*P*	*P* of model fit[a]
1	Intervention (ref.: paring alone)	1.64	0.62–4.38	0.32	0.80
2	Intervention (ref.: paring alone)	1.80	0.66–4.93	0.25	0.48
	Total number of warts at entry	1.06	0.90–1.19	0.26	
	Number of locations of warts at entry	1.09	0.48–2.47	0.84	
	Sex (ref.: male sex)	0.70	0.25–1.96	0.50	
	Age, years	0.99	0.96–1.03	0.90	

The odds ratio (OR) is the ratio of the odds of wart clearance and the odds of no clearance of warts after treatment intervention.
Analysis 1: Intervention is the only covariate in the model.
Analysis 2: The number of warts and locations of warts prior to the first intervention was included along with patient age and sex as covariates in the model.
[a]A high *P*-value indicates a satisfactory model fit to the data.

TABLE 4. Patient Assessed Pain Subsequent to Interventions

Pain evaluated in relation to treatment session	Paring plus IPL, median (range)	Paring, median (range)	*P*
First session	6.0 (1.0–10.0)	0 (0.0–5.0)	<0.0005
Third session	5.3 (0.5–10.0)	0.0 (0.0–7.0)	<0.0005
Change in pain before first and third treatment	0 (−5.5–3.0)	0 (−8.0–7.5)	0.06
Change in pain after first to third treatment	0 (−6.5–3.5)	0 (−4.0–4.0)	0.13

Pain was assessed on a numeric scale from 0 = no pain and 10 = worst imaginable pain. Range (min value–max value).

developed hypo- or hyperpigmentation or scarring post-treatment. IPL patients reported more pain and as this is a patient-reported outcome and patients were not blinded to intervention we cannot tell if this pain was real or perceived [19–21]. However, pain of mild to moderate intensities related to IPL is a known adverse effect [23–25]. The IPL-system used in this trial did not use cooling of the epidermis, which is utilized in newer IPL-systems to minimize treatment-related pain [22–25].

In conclusion, the present randomized clinical trial used a specific IPL device at specific settings and found no significant different in treatment outcome of paring plus IPL versus paring alone for recalcitrant hand and foot warts. Although both treatments were safe, patients experienced moderate pain after paring plus IPL compared to paring alone.

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