Liquid nitrogen cryotherapy *versus* 70% trichloroacetic acid in the treatment of anogenital warts: A randomized controlled trial

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Background: Cryotherapy is one of the most common and effective treatments of anogenital warts, and trichloroacetic acid is one of the methods commonly used. The aim of this study was to compare the effect of cryotherapy and trichloroacetic acid in the treatment of anogenital warts.

Methods: This randomized clinical trial was conducted on patients with anogenital warts. The patients were divided into two groups; one group was treated with liquid nitrogen and the other with 70% trichloroacetic acid. In both groups, the treatment was done every two weeks until complete disappearance of the lesions or for 6 sessions.

Results: In this study, 68 patients with anogenital warts were studied. After the 6th session, the cure rate of in the patients treated with trichloroacetic acid (94.1%) was higher than the patients treated with cryotherapy (85.3%) (P>0.05).

Conclusion: It seems that cryotherapy and trichloroacetic acid therapy have similar results in the treatment of anogenital warts.

Keywords: anogenital warts, cryotherapy, trichloroacetic acid

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INTRODUCTION

Human papilloma viruses belong to a large family of DNA viruses that cause warts. Among several clinical patterns of warts, anogenital warts have several important concerns: they are one of the most common sexual transmitted infections (STI), they may indicate the presence of other concomitant STIs, infection with high risk HPV is an important risk factor for anogenital cancers, and vertical transmission from the mother to the child can occur during delivery [1-3].

There are several reatment methods and their selection depends on several factors such as age, sex, patient's and physician's choice of cytotoxic or antiviral agents, physical destruction,

immunomodulators, or systemic drugs. Cryotherapy and trichloroacetic acid (TCA) (70% to 90%) are two physical destruction methods [1,2]. The aim of this study was to compare the effect of cryotherapy and 70% TCA in the treatment of anogenital warts.

PARTICIPANTS AND METHODS

This randomized clinical trial (RCT) was conducted on the patients with anogenital warts that were visited in two hospitals in Mashhad, Iran (Ghaem and 22 Bahman Hospitals) from 21 January 2007 to 23 September 2010. Exclusion criteria were: 1) receiving other treatments during the last 3 weeks, 2) pregnancy, 3) immune deficiency due to other diseases and taking drugs, 4) anogenital warts that did complete the treatment course, 5) unwillingness to participate in study, 6) receiving other medicines such as zinc sulfate, cimetidine, or levamisole for anogenital warts during the last month. The age of the patients, duration of the disease, clinical type of the wart (condyloma, small papules, and common wart like lesions) and the location of lesions were recorded. The patients were advised to use condoms during the course of treatment and follow-up. In this study, we used stratified randomization to allocate patients to two groups. One of the two groups was randomly treated with liquid nitrogen (cryotherapy) and the other group received %70 liquid TCA. In the first group, liquid nitrogen was applied for 10 to 15 seconds (according to the size of the lesion until a narrow white rim of about 1 mm appeared around it) on each wart by an applicator every two weeks. In the second group, the warts were treated with %70 liquid TCA. This solution was applied to the wart by an applicator, and we asked the patients to wash their warts with water or normal saline after 20 minutes; this treatment was repeated every two weeks. For ulceration during these two weeks, the patients in both groups received topical povidone iodine. The patients were treated until the disappearance of the warts or for a total of 6 sessions. In order to know whether the warts recurred, the patients were examined in the 1 and 3 months after the end of treatment. Cure and recurrence were evaluated clinically as the disappearance or presence of the lesions. To evaluate the pain and burning sensation during and also 3 days after the treatment, the patients were asked to describe their pain and burning on a scale of 0 to 10. The declared scores were placed in 4 different categories (0= no pain, 1-3= weak pain, 4-7= moderate pain, 8-10= severe pain). Data was analyzed with SPSS software version 11.5 using the chi square, Fisher's exact, independent *t*, and Mann Whitney *U* tests. Informed consent was obtained from the participants before the study.

RESULTS

During the study period, 72 patients with

Table 1. Distribution of the age and gender of the patients, and number, clinical type, location, and duration of the lesions in the treatment groups

	Cryotherapy	TCA	*P*
No. of patients	34	34	—
Female	17	17	—
Male	17	17	—
Age (years) (mean±SD)	31.1±8.9	29.2±9.4	0.393
Number of the lesions (mean ± SD)	12.7±9.2	12.7±9.8	0.98
Clinical type of warts			
Condyloma	8 (47.1%)	9 (52.9%)	
Small papule	33 (49.3%)	34 (50.7%)	0.99
Common wart-like lesion	1 (100.0%)	0 (0.0%)	
Location of lesions			
Genital area	31 (52.5%)	28 (47.5%)	
Perianal area	2 (22.2%)	7 (77.8%)	0.235
other	18 (50.0%)	18 (50.0%)	
Duration of lesions			
1 month	5 (35.7%)	9 (64.3%)	
2-6 months	18 (47.4%)	20 (52.6%)	0.236
> 6 months	11 (68.8%)	5 (31.2%)	

anogenital warts were detected, of whom 4 were excluded because they were not willing to participate in the study. Therefore, 68 patients were evaluated of whom 34 were treated with cryotherapy (%50) and 34 were treated with TCA. The mean age of the patients was 30.2±9.2 years. The mean age of men (32.1±8.9 years) was higher than the women (28.2±9.2 years) (*P*=0.078). The mean age of the patients was 31.1±8.9 years in the cryotherapy group and 29.2±9.4 years in the TCA group. The demographic data of the patients are shown in Table 1. Seventy-three percent of the patients were married and the rest of them were single. At the beginning of the study, the duration of the disease was less than 6 months in 67.6% and more than 6 months in 32.4% of the patients. Thirty three of the patient's couples (% 66.0) had anogenital warts. The number of warts ranged from 2 (in 3 patients) to approximately 50 (in two patients) with a median of 10. At the end of the 6th session, the cure rate in the TCA group was higher (%94.1) than the cryotherapy group (%85.3) although the difference was not statistically significant (*P*=0.231). Recurrence was seen in nine patients (%13.2) in the first month after the treatment and in one patient (%1.5) in the 3rd month after the treatment (Table 2). This study showed that from the 1st to the 6th session, the score of burning and pain reduced in both methods (both during treatment and 3 days after the beginning of the treatment) (Table 3).

DISCUSSION

Taner *et al.* studied the effect of 85% TCA on treating genital warts in women and observed that all the warts were cured after finishing the treatment course in an average of 4 (2-5) sessions [4]. Roongpisuthipong *et al.* found observed that 40.7% of the women treated with TCA were completely cured [5].

In two separate studies, Abdullah *et al.* and Damstra *et al.* reported that the use of TCA resulted in clearance rates of 70% and 96% after six applications, respectively [6,7]. Cryotherapy is quick, easy, safe, and relatively inexpensive [8,9]; thus, cryotherapy is the first line treatment for genital warts in pregnant women and in patients who tolerate the pain associated it [8]. Some studies have shown that cryotherapy is superior to TCA therapy [6,7,10]. In a survey of more than 489 patients by Pirottaet in Australia to study the treatment methods of external genital warts, about 50% of the patients were cured after the first session and no considerable difference was observed between different treatment methods, including TCA and cryotherapy [11]. The findings of this study are similar to our results.

In our study, the recurrence rate of warts until three months after the cure was studied and as observed in Table 2, the majority of the recurrences occurred in first the treatment. Abdullah *et al.* observed complete clearance of lesions 3 months after treatment in 86% of patients receiving cryotherapy and 70% of those receiving TCA [6]. There were no recurrences in the study conducted by Taner *et al.* in Turkey to find the effect of TCA 85% on external genital warts in women, but recurrence was observed in 17.6% of the patients in the second 6 months [4]. Although some studies have shown that TCA is less effective than cryotherapy for the treatment of anogenital warts, we observed that the cure rate was rather higher in the group treated with TCA than the group receiving cryotherapy at the end of the 6th session but this difference was not statistically significant. Therefore, it seems that cryotherapy and TCA have similar results in the treatment of anogenital warts.

Table 2. Frequency of the recurrence of the warts according to type of treatment, gender, and marital status

		Recurrence one month after the treatment n (%)	Recurrence 3 months after the treatment n (%)	Total N (%)
Type of treatment	TCA	5 (14.7)	1 (2.9)	6 (17.6)
	Cryotherapy	4 (11.8)	0 (0)	4 (11.8)
Gender	Man	7 (20.6)	0 (0)	7 (20.6)
	Woman	2 (5.9)	1 (2.9)	3 (8.82)
Marital status	Single	2 (11.1)	0 (0)	2 (11.1)
	Married	7 (14)	1 (2)	8 (16)

Table 3. Frequency of pain and burning during and 3 days after the treatment according to treatment sessions

Session #			Degree of pain and burning				*P*
			0 (No pain)	1-3 (Weak)	4-7 (Moderate)	8-10 (Severe)	
			n (%)	n (%)	n (%)	n (%)	
1st	During treatment	TCA	0 (0)	12 (35.3)	22 (64.7)	0 (0)	0.07
		Cryotherapy	0 (0)	3 (8.8)	29 (85.3)	2 (5.9)	
		Total	0 (0)	15 (22.1)	51 (75)	2 (2.9)	
	After 3 days	TCA	12 (35.3)	20 (58.8)	2 (5.9)	0 (0)	0.415
		Cryotherapy	10 (29.4)	19 (55.9)	5 (14.7)	0 (0)	
		Total	22 (32.4)	39 (57.3)	7 (10.3)	0 (0)	
2nd	During treatment	TCA	1 (2.9)	11 (32.4)	22 (64.7)	0 (0)	0.04
		Cryotherapy	1 (2.9)	4 (11.8)	27 (79.4)	2 (5.9)	
		Total	2 (2.9)	15 (22.1)	49 (72.1)	2 (2.9)	
	After 3 days	TCA	13 (38.2)	20 (58.8)	1 (2.9)	0 (0)	0.321
		Cryotherapy	11 (32.4)	18 (52.9)	5 (14.7)	0 (0)	
		Total	24 (35.3)	38 (55.9)	6 (8.8)	0 (0)	
3rd	During treatment	TCA	12 (35.3)	6 (17.6)	16 (47.1)	0 (0)	0.083
		Cryotherapy	8 (23.5)	3 (8.8)	21 (61.8)	2 (5.9)	
		Total	20 (29.4)	9 (13.2)	37 (54.4)	2 (2.9)	
	After 3 days	TCA	18 (52.9)	15 (44.1)	1 (2.9)	0 (0)	0.91
		Cryotherapy	18 (52.9)	13 (38.2)	3 (8.8)	0 (0)	
		Total	36 (52.9)	28 (41.2)	4 (5.9)	0 (0)	
4th	During treatment	TCA	29 (85.3)	1 (2.9)	4 (11.8)	0 (0)	0.02
		Cryotherapy	20 (58.8)	3 (8.8)	10 (29.4)	1 (2.9)	
		Total	49 (72.1)	4 (5.9)	14 (20.6)	1 (1.5)	
	After 3 days	TCA	29 (85.3)	5 (14.7)	0 (0)	0 (0)	0.28
		Cryotherapy	26 (76.5)	5 (14.7)	3 (8.8)	0 (0)	
		Total	55 (80.9)	10 (14.7)	3 (4.4)	0 (0)	
5th	During treatment	TCA	32 (94.1)	0 (0)	2 (5.9)	0 (0)	0.673
		Cryotherapy	30 (88.2)	1 (2.9)	3 (8.8)	0 (0)	
		Total	62 (91.1)	1 (1.5)	5 (7.4)	0 (0)	
	After 3 days	TCA	32 (94.1)	2 (5.9)	0 (0)	0 (0)	0.999
		Cryotherapy	32 (94.1)	1 (2.9)	1 (2.9)	0 (0)	
		Total	64 (94.1)	3 (4.4)	1 (1.5)	0 (0)	
6th	During treatment	TCA	34 (100)	0 (0)	0 (0)	0 (0)	0.493
		Cryotherapy	32 (94.1)	2 (5.9)	0 (0)	0 (0)	
		Total	66 (97.1)	2 (2.9)	0 (0)	0 (0)	
	After 3 days	TCA	34 (100)	0 (0)	0 (0)	0 (0)	0.999
		Cryotherapy	33 (97.1)	1 (2.9)	0 (0)	0 (0)	
		Total	67 (98.5)	1 (1.5)	0 (0)	0 (0)	

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