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10.21608/zumj.2020.22633.1708**ORIGINAL ARTICLE****Comparative study of efficacy of *Candida albicans* antigen immunotherapy and cryosurgery in the treatment of common warts**¹ Enayat Attwa, ² Rehab Elawady, ³ Eman Salah^{1,3} Dermatology, Venereology and Andrology department, Faculty of Medicine Zagazig University.² Dermatology department, Elsharkia Zagazig Egypt.**Corresponding author:**Rehab Elawady,
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rehab.elawady77@icloud.comSubmit Date 2020-02-09
Revise Date 2020-04-05
Accept Date 2020-04-08**ABSTRACT**

Background: Infections with human papillomavirus (HPV) are the third basic skin ailment experienced. Verrucae are considerate epithelial expansions of skin and mucosa achieved by infection with HPV. No treatment works for all verrucae on all patients, however numerous choices are accessible, and, with time and tolerance, most verrucae will react to treatment. In this study, we compared the efficacy of immunotherapy by *Candida albicans* antigen injection and cryosurgery on Verrucae lesions.

Methods: A clinical trial was done with forty patients with verruca vulgaris; they were randomly divided into two groups. First group received intralesional injection of 0.3ml of *candida albicans* antigen repeated every 2 weeks until complete improvement of all warts or for a maximum of five sessions. The second group was treated by cryosurgery with liquid nitrogen at two weeks interval for a maximum of five sessions or until clearance of all lesions.

Results: The patients showed a highly significant therapeutic response to cryosurgery compared to immunotherapy ($P < 0.001$). 40% of patients were completely cured with cryosurgery, while only 25% responded to immunotherapy.

Conclusions: Cryosurgery is an effective treatment of warts. This method has a better therapeutic response than the intralesional *Candida* antigen in the treatment of multiple common warts.

Key words: Cryosurgery, *Candida* antigen, Immunotherapy, Warts.

**INTRODUCTION**

Warts are disease of keratinocytes by human papilloma virus. Causing benign skin lesion with discomfort and embarrassment, Hands, feet, face, and genitalia are the main predilection sites [1].

Warts have different clinical forms. Several therapeutic methods are used including cryosurgery, surgical excision, electro cautery, and laser, intralesional injection of mumps, measles, rubella (MMR) antigens, purified protein derivatives (PPD), *Candida albicans*, and bleomycin [2]. Despite the various modalities, No treatment has an exceptionally high achievement rate. A "Keep a watch out" approach is better particularly in asymptomatic cases as numerous of these lesions disappear spontaneously. Preferably, the treatment must be cheap and simple with the least probability of adverse effects [3].

Cryosurgery by liquid nitrogen is commonly used to eradicate warts via necrotic destruction of HPV-infected Keratinocytes or by inducing cell-mediated immune response [4]. Intralesional immunotherapy stands another current therapeutic approach that enhances the immune system through the delayed type hypersensitivity response and afterwards clearing the HPV. Injection with *Candida* antigen is a non invasive technique with minimal adverse effects [5, 6].

METHODS

Study design: this was a clinical trial

Administrative and ethical design: The Institutional Review Board and ethical of Zagazig University Hospital approved this study (with approval number 5193/5-2-2019).

All subjects received information about the purpose and the research technique, and then an

informed consent was obtained if they accepted to participate.

This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Study setting: This study was conducted in Dermatology, Venereology & Andrology Department; Faculty of medicine, Zagazig University Hospital

Study period: from February 2019 till September 2019.

Inclusion criteria: Adult patient more than 18 years of age with multiple common warts, without any coexisting systemic treatments, were included in the study.

Rejection criteria: Pregnancy, lactation, immunodeficiency, HIV infection, hypersensitivity to Candida antigen or to cold, and any history of allergic dermatological diseases or bronchial asthma.

Study groups: Forty patients were allocated to 2 groups (20 in each group). Group (A) treated by injection of 0.3 ml of *Candida albicans antigen* intralesionally, however Group (B) received liquid nitrogen cryosurgery, all at 2 week interval till complete response was achieved or for five sessions.

Operational design: A detailed history, clinical examination was done for every case to determine type, number, sites of warts, and size of the warts. Response to treatment was assessed by reduction in size, number of warts and returning to normal skin marking with photographic evaluation at base line and at each session. Immediate and late adverse effects of both Candida antigen injection and cryosurgery were also evaluated after each treatment visit. The clinical response to treatment was assessed as follows: no / slight response (< 25% reduction in the size of verruca), moderate response (25 – 75% reduction), near the complete response (76 – 99% reduction), and complete cure (disappearance of all warts) [7].

STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) and Med-Calculator 13 for windows (MedCalc Software bvba, Ostend, Belgium). Quantitative data were expressed as the mean \pm SD & median (range) and qualitative data were stated as absolute frequencies (number) & relative frequencies (percentage). Continuous informations

were checked for normality by Shapiro Walk test. P value < 0.05 was considered statistically significant.

RESULTS

This study had been conducted on 40 patients (24 females and 16 males) with multiple common warts (i.e. total number of warts in all patients was 392 warts).

Patients were divided into equal groups (A, B) of twenty patients each. Their ages ranged from 18 to 68 years, by a mean of 35.35 years in Group (A) (treated by Candida Antigen), and from 18-48 years with a mean of 28.05 years in Group (B) (treated with Cryosurgery).

No statistically significant difference was founded between the studied groups as regards as age, sex or skin type (**Table 1**).

The number of warts was highly statistically significant different among all groups, which range between (3-50 warts) with a mean of 11.70 ± 10.42 in Group (A), and range between (3-10warts) with a mean of 4.65 ± 1.87 in Group (B), also a highly statistically significant difference were found between two groups regarding surface area of all warts (**Table 1**).

In the immunotherapy group, a complete remission was achieved in 5 patients (25%), moderate response in 4 patients (20%) and no response in 11 patients (55%). While In the cryosurgery group (B), complete clearance was observed in 8 patients (40%), marked response in 2 patients (10%), moderate response in 7 patients (35%) and no response in 3 patients (15%), Patients showed a significantly better response to cryosurgery compared to immunotherapy ($P=0.003$) (**Table 2**), that may indicate a greater efficacy for cryosurgery versus Candida antigen injections that also display on bar chart in (**Figure 1**).

Regarding sequels to treatment, a highly statistically significant difference was found between the studied groups. In group (A) pain happened in all patients (100%), headache in 16 patients (80%), edema and swelling occurred in 17 patients (75%), fever and myalgia in happened in 13 patients (65%), erythema in 9 patients (45%), and no bullae formation. While Group (B) the most common sequels were pain (95%), bullae formation (70%), erythema (25%), and skin hypopigmentation (15%), and none of the patients complained of neither fever myalgia nor headache (**Table 3**).

Table 1

Demographic data	Group A (N=20)		Group B (N=20)		Test	p-value (Sig.)
	No.	%	No.	%		
Sex						
Male	6	30%	10	50%	1.783§	0.410 (NS)
Female	14	70%	10	50%		
Age (years)						
Mean ± SD	35.35±13.89		28.05 ± 7.45		2.262*	0.113 (NS)
Median (Range)	33.50 (18 – 68)		28.50 (18 – 48)			
Skin photo type(Fitz-patric)						
Type II	0	0%	1	5%	3.795§	0.704 (NS)
Type III	13	65%	10	50%		
Type IV	7	35%	9	45%		
Type V	0	0%	0	0%		
Patient complain						
Pain	0	0%	1	5%	6.103§	0.192 (NS)
Cosmetic disfigurement	10	50%	6	30%		
Fear of spread	10	50%	13	65%		
Disease duration (months)						
Mean ± SD	17.35 ± 14.39		12.10 ± 8.53		1.564•	0.457 (NS)
Median (Range)	12 (5 – 60)		12 (2 – 36)			
Number of warts						
Mean ± SD	11.70 ± 10.42		4.65 ± 1.87		23.850•	<0.001 (HS)
Median (Range)	8 (3 – 50)		4 (3 – 10)			
Site of wart						
Neck	1	5%	0	0%	6.415§	0.378 (NS)
Hand	16	80%	20	100%		
Leg	1	5%	0	0%		
Dorsum of the feet	2	10%	0	0%		
Previous wart infection (past history)						
Yes	11	55%	5	25%	5.275	0.072 (NS)
No	9	45%	15	75%		

Table 2

Response to treatment	Group A (N=20)		Group B (N=20)		Test	p-value (Sig.)
	No.	%	No.	%		
Wart size reduction after all sessions (%)						
Mean ± SD	42.50 ± 37.95		70.25 ± 32.01		10.137•	0.006 (S)
Median (Range)	25 (10 – 100)		77.50 (0 – 100)			
Size of largest wart (mm) after all sessions						
Mean ± SD	3.35 ± 2.73		1.85 ± 2.49		4.166•	0.125 (NS)
Median (Range)	3 (0 – 10)		0.50 (0 – 9)			
Response						
No/minimal	11	55%	3	15%	20.083§	0.003 (S)
Moderate	4	20%	7	35%		
Marked	0	0%	2	10%		
Complete	5	25%	8	40%		

Table 3

Sequels of treatment	Group A (N=20)		Group B (N=20)		Test§	p-value (Sig.)
	No.	%	No.	%		
<u>Erythema</u>						
Present	9	45%	5	25%	17.813	<0.001 (HS)
Absent	11	55%	15	75%		
<u>Edema/Swelling</u>						
Present	17	85%	5	25%	30.000	<0.001 (HS)
Absent	3	15%	15	75%		
<u>Pain</u>						
Present	20	100%	19	95%	2.034	0.362 (NS)
Absent	0	0%	1	5%		
<u>Bullae</u>						
Present	0	0%	14	70%	39.192	<0.001 (HS)
Absent	20	100%	6	30%		
<u>Fever</u>						
Present	13	65%	0	0%	26.652	<0.001 (HS)
Absent	7	35%	20	100%		
<u>Myalgias</u>						
Present	13	65%	0	0%	26.652	<0.001 (HS)
Absent	7	35%	20	100%		
<u>Headache</u>						
Present	16	80%	0	0%	46.667	<0.001 (HS)
Absent	4	20%	20	100%		

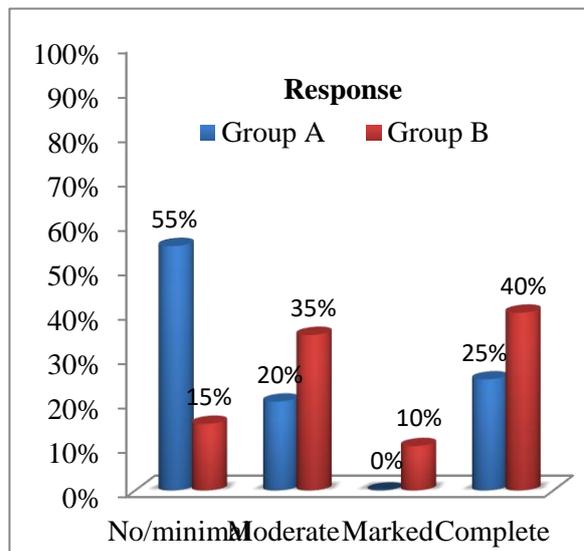


Figure 1



Figure 2

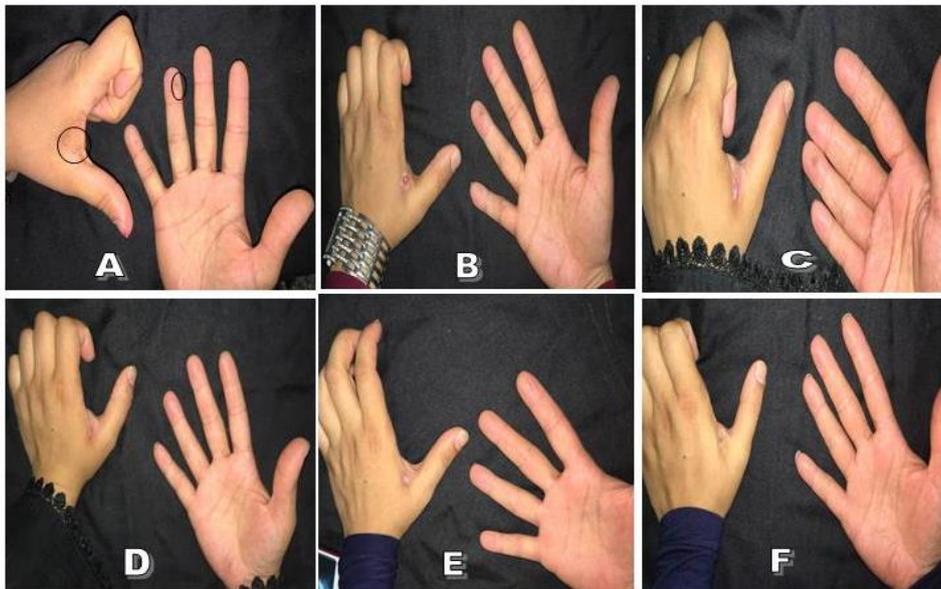


Figure 3

DISCUSSION

Numerous methods have been used in treating warts; no single treatment has been revealed to be effective in a complete remission, the current main therapeutic options for warts include the destruction of visible lesions by physical or chemical methods and immunomodulation therapies [8].

Immunotherapy induces strong cell-mediated immune reaction to alter the balance between Th1 and Th2 responses leading to eradication of HPV [9]. Cryosurgery causes local destruction of HPV-infected keratinocytes and immunological effects through Natural killer cell cytotoxicity [10].

Therefore, in this study, we compared cryosurgery over immunotherapy two therapeutic approaches representing a potential clinical response for treating warts.

In the presented work, we directly injected Candida antigen into the largest wart, we did not perform a pre-sensitizing injection at the volar surface of the arm because almost all patients were expected to be immune based on the high incidence of Candida infection in our community as similarly suggested by other authors [9,11].

In the presented work, 25 % of patients of the Candida antigen injected group revealed complete clearance which was similar to the study of Majewski and Jablonska [12], but noticed to be

inferior to results from similar studies, which have reported different therapeutic responses, ranging from 47% to 87%, for immunotherapy in the treatment of warts [6,13-14]. However, those studies included different injection regimens regarding the manufacturer of the antigen, the amount and concentration of the injected antigen per session in addition to the different time intervals between sessions and the total number of given treatment sessions. Also, factors related to the treated warts such as the clinical type, number, site, size, duration, degree of HPV resistance and different HPV serotypes may also be responsible for the variable responses to *Candida albicans* antigen [15].

We faced some practical difficulties though performance the intralesional injections. The most important is the possibility of the intralesional drug to ooze out of the wart while injecting. To overcome this problem, it is better to inject the wart from the upper surface and not from the lateral side.

At present, cryosurgery is preferred as the first-line of the treatment. 40% of cryosurgery Group showed complete clearance which was also lower than success rates reported by other studies [16-17], as according to **Ahmed et al.** [18], efficacy of cryosurgery in clinical trials is varied between 9 to 87 % (mean 49%). The efficacy of cryosurgery depends on wart type, cryogen type, mode of application, freezing time, number of freezing/thawing cycles, and frequency of treatment sessions [19].

Comparing both groups, there was statistically significant difference in complete clearance rates between the candida antigen group (25%) and the cryosurgery groups (40 %) that reveal that cryosurgery treatment are better than immunotherapy. Which against the similar study of **Khozeimeh et al.** [20] that shown that immunotherapy was higher efficacy than cryosurgery. That difference may produced by different time intervals between sessions and the total number of given treatment sessions, also type of warts treated.

Fortunately, we did not encounter any significant side effects in our patients except for the pain during the procedure in almost all patients in both groups, while flu-like syndrome in 65% of the patients of the immunotherapy group, and bullae formation in (70%) of cryosurgery group. These adverse effects were very tolerable and did not necessitate stopping the treatment.

The limitation of our study was small sample size, so, we recommend larger clinical trial in order to better assessment response rate and side effects.

CONCLUSION

Cryosurgery treatment is superior to immunotherapy in the treatment of common warts, more effective for physicians and can save time and cost.

REFERENCES

- [1] **Rowson KE, Mahy BW.** Human papova (wart) virus. *Bacteriol Rev.* 1967; 31(2): 110–131.
- [2] **Gibbs S, Altman D, Harvey I, Sterling J, Stark R.** Papers Local treatments for cutaneous warts: systematic review Commentary: systematic reviewers face challenges from varied study designs. *BMJ.* 2002; 325(7362): 461.
- [3] **Van Huijsduijnen RH, Alblas S, De Rijk R, Bol JF.** Induction by salicylic acid of pathogenesis-related proteins and resistance to alfalfa mosaic virus infection in various plant species. *J Gen Virol.* 1986; 67(10): 2135–2143.
- [4] **Jaiswal P, Dhali TK, & D'souza P.** Comparitve study of efficacy of radiofrequency ablation, electodesiccation, and Cryosurgery in the treatment of cutaneous warts. *J Dermatol.* 2019; 23(1), 24.
- [5] **Silverberg NB, Lim JK, Paller AS, Mancini AJ.** Squaric acid immunotherapy for warts in children. *J Ame Acad Dermatol.* 2000; 42(5 pt 1):803–808.
- [6] **Maronn M, Salm C, Lyon V, Galbraith S.** One-year experience with candida antigen immunotherapy for warts and molluscum. *Pediatr Dermatol.* 2008; 25(2):189–192.
- [7] **Abou-Taleb DAE, Abou-Taleb HA, El-Badawy O, Ahmed AO, Thabiet Hassan AE, Awad SM.** Intralesional vitamin D3 versus intralesional purified protein derivative in treatment of multiple warts: A comparative clinical and immunological study. *Dermatol Ther.* 2019; 32(5):e13034.
- [8] **Lee AN, Mallory SB.** Contact immunotherapy with squaric acid dibutylester for the treatment of recalcitrant wart. *J Am Acad Dermatol.* 1999;41:595-599.
- [9] **Nofal A, Salah E, Nofal E, Yosef A.** Intralesional antigen immunotherapy for the treatment of warts: current concepts and future prospects. *Am J Clin Dermatol.* 2013; 14(4); 253-260.
- [10] **Abeck D, Tetsch L, Luftl M, Biedermann T.** Extragenital cutaneous warts - clinical presentation, diagnosis and treatment. *J Dtsch Dermatol Ges.* 2019; 17(6), 613-634.
- [11] **Maronn M, Salm C, Lyon V, Galbraith S.** One-year experience with candida antigen immunotherapy for warts and molluscum. *Pediatr dermatol.* 2008; 25(2), 189-192.

[12] **Majewski S, Jablonska S.** Human papillomavirus-associated tumors of the skin and mucosa. *J Am Acad Dermatol.* 1997; 36:659-685.

[13] **Clifton MM, Johnson SM, Roberson PK, Kincannon J, Horn TD.** Immunotherapy for recalcitrant warts in children using intralesional mumps or Candida antigens. *Pediatr Dermatol.* 2003; 20(3): 268–271.

[14] **Nofal A, Nofal E.** Intralesional immunotherapy of common warts: successful treatment with mumps, measles and rubella vaccine. *J Eur Acad of Dermatol Venereol.* 2010; 24(10): 1166–1170.

[15] **Nofal A, Marei A, Amer A, Amen H.** Significance of interferon gamma in the prediction of successful therapy of common warts by intralesional injection of Candida antigen. *Int J of Dermatol.* 2017; 56(10): 1003-1009.

[16] **Bourke JF, Berth-Jones J, Hutchinson PE.** Cryotherapy of common viral warts at intervals of 1, 2 and 3 weeks. *Br J Dermatol.* 1995;132(3): 433-436.

[17] **Bruggink SC, Gussekloo J, Berger MY, Zaaier K, Assendelft WJ, de Waal MW, et al.** Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care; randomized controlled trial. *CMAJ.* 2010;182(15): 1624-1630.

[18] **Ahmed I, Agarwal S, Ilchyshyn A, Charles-Holmes S, Berth-Jones J.** Liquid nitrogen cryotherapy of common warts: cryo-spray vs. cotton wool bud. *Br J of Dermatol.* 2001; 144(5): 1006-1009.

[19] **Walczuk I, Eertmans F, Rossel B, Cegielska A, Stockfleth E, Antunes A, Adriaens E.** Efficacy and safety of three cryotherapy devices for wart treatment: A Randomized, Controlled, Investigator-Blinded, comparative study. *Dermatol Ther.* 2018; 8(2): 203-216.

[20] **Khozeimeh F, Jabbari Azad F, Mahboubi Oskouei Y, Jafar M, Tehranian S, Alizadehsani R, Layegh P.** Intralesional immunotherapy compared to cryotherapy in the treatment of warts. *Int J Dermatol.* 2017; 56(4); 474-478

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