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The efficacy and safety of intralesional bee venom injection Vs intralesional candida injection in treatment of Common Warts

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Warts are a common sight in dermatology OPDs and they constitute the commonest cutaneous manifestation of human papilloma virus (HPV) infection. A variety of modalities has been used and treatment may be invasive and/or conservative. Therefore, the aim of this study was to evaluate the efficacy and safety of intralesional Bee venom injection versus intralesional Candida antigen injection in the treatment of common warts. At a hospital-based, adult, outpatient dermatology clinic, 28 patients with common warts of the hands and feet ***14*** patients of them were treated with intralesional candida antigen and the other 14 patients were treated with intralesional Bee venom injection. This study included 8 males and 20 females with age ranged from 17 to 60 years. Side effects as well as improvements in texture after each session and after the final treatment were documented. The patients treated maximum for 5 sessions for 5 weeks or less if complete recovery occurs. Patient's response to treatment was assessed clinically and the results of the present study revealed complete clearance of the injected warts in 7 patients (50%) and partial response in 7 patients (50%) in bee venom. In the second group treated by candida, complete clearance of the injected warts was observed in 5 patients (35.7%) and partial response in 9 patients (64.3%), however, no statistically significant difference was observed between the two groups. We noted comparable side effects and they were mild, tolerable, and transient and did not necessitate stoppage of treatment in any of the studied patients and no recurrence between the two groups.Intralesional Candida injection is a promising effective and safe modality for the treatment of common warts.

Keywords: Warts, Candida injections, Bee venom injection, Immunotherapy.

INTRODUCTION

Common Warts or Verrucae Vulgaris are benign proliferations of the skin or mucosa caused by infection with human papilloma virus (HPV), They are commonly caused by HPV-2 and commonly situated on the back of hands and fingers but also may occur anywhere on the skin Saini et al.,2016 Infection with HPV occurs by direct skin contact with sites of trauma. The incubation period is approximately two to six months Diagnosis is made by examination and observation of typical features. Investigations are not usually required or appropriate Radley et al., 2016

Warts are usually treated by traditional treatments as destructive modalities such as cryotherapy, electrocoagulation, chemical cautery, and laser. All of these treatments can be painful, time consuming or expensive and none of them is considered the gold standard Gharib et al., 2015

Candida is the first antigen that was tried for immunotherapy of warts and reported success in majority of patients. Candida immunotherapy has even been reported in all body warts even genital

warts and also in children with recalcitrant warts King et al., 2005

Bee venom or apitoxin is amixture of proteins, melittin (main component 52%), apamin, adolapin, phospholipase A2, hyaluronidase, histamine, dopamine and protease inhibitor. Bee venom has been found to be effective in several inflammatory and viral diseases. It has anti-inflammatory and anti-oxidant effects Son et al., 2007

The present study was aimed to evaluate the efficacy and safety of intralesional Bee venom injection vs intralesional Candida antigen injection in the treatment of common warts.

MATERIALS AND METHODS

The present study was carried at Dermatology, Venereology and Andrology department, Zagazig University Hospitals. All patients were recruited from Dermatology, Venereology and Andrology outpatient clinics of Zagazig University Hospitals in the period from February 2017 to February 2018.

The present study included 28 adult patients of both sexes with common warts of different sites, sizes and durations and no concurrent use of systemic or topical treatments of warts. After excluded patients with hypersensitivity to Candida antigen or Bee venom, acute febrile illness, immunosuppressive diseases e.g. systemic lupus erythematosus, concomitant intake of immunosuppressive, past history of allergic skin disorders such as generalized eczema or urticarial and history of meningitis or convulsions, pregnancy and lactation. Written Informed consent was taken from the patient to participate in the study. Approval for performing the study was obtained from internal medicine Department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval.

Patients were divided into two groups: group 1: Included 14 patients with common warts who received intralesional injection with purified Bee venom. Group 2: Included 14 patients with common warts who received intralesional injection with Candida albicans antigen.

Patients were subjected to history taking regarding age and sex, history of present dermatological disease: including, onset, course, duration, site, and history of previous treatment for the disease, and history of associated other dermatological diseases, and history of systemic diseases and drug intake. Local examination was cared for warts to determine the type, number, size, sites of warts and the presence or absence of distant lesions. The diagnosis of warts was made by clinical examination, and patients were advised not to use any other wart treatment during the study period.

In the Bee venom group: all 14 patients were tested before the first injection with Purified Bee venom to exclude allergic patients to bee venom. Patients with negative skin test response were injected with 0.1 ml of Purified Bee venom (Lypophilized Apis Mellifera Purified Bee Venom 1.0mg and Sodium Chloride 9mg that brought from Egyptian organization for biological products and vaccines (VACSERA) in Cairo, Egypt) into the largest wart using an insulin syringe, which is held parallel with the skin surface with the bevel facing upward. Injections were done at 1-week intervals until complete clearance was achieved or for a maximum of five treatment sessions.

In the Candida group: all 14 patients were directly injected with 0.1 ml of 1/1000 solution of Candida antigen (Candida albicans 1:20 w/v 10 ml vial that was brought from Allergy Laboratories, INC. Oklahoma City, USA) into the largest wart using an insulin syringe, which is held parallel with the skin surface with the bevel facing upward. Injections were done at 1-week intervals until complete clearance was achieved or for a maximum of five treatment sessions. Response to treatment in both groups was evaluated by the decrease in size of warts and photographic comparison at base line and at each visit. Immediate and late adverse effects of both antigens were also evaluated after each treatment session.

The results were evaluated as follows; Complete response: disappearance of the wart and return of the normal skin markings. Partial response: 50-99% reduction in wart size and no response: 0-49% decrease in wart size. Follow up evaluation was done every month for six months after completion of the treatment for detection of any wart recurrence.

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 24.0 for windows (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. Independent T test and

Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates Non-significant difference.

RESULTS AND DISCUSSION

The 28 patients included 8 males and 20 females with ages ranged from 17 to 60 years old. Regarding demographic data and warts features, we found no significant difference.

Warts treatment represents a problem for both patients and physicians. Most of the current modalities such as cryotherapy, electrodessication and laser therapy depend on the ablation of warts, and they are commonly associated with significant pain, tissue destruction and high recurrence rate Gharib et al., 2015, Kim et al., 2013 and Aldahan et al., 2016

Several immunotherapeutic agents have been used for the treatment of warts to overcome the challenges associated with the use of destructive therapies. Among these agents, is the recently used intralesional antigen immunotherapy that has shown a promising efficacy and safety in the treatment of different types of warts Eassa et al., 2011, Abd-Elazeim et al., 2014 and Nofal et al. , 2017

Melittin, which is the main component of bee venom, was found to have antiviral activities caused by specific intracellular events as selective reduction of biosynthesis of some viral proteins as reported on herpes virus-1 and HIV-1 infected lymphoma cells Moreno, and Giralt, (2015 Bee venom has been found to be effective in the treatment of localized plaque psoriasis with minimal side effects Hegazi et al., 2013

Based on the previous observations, we designed our study to evaluate the efficacy and safety of intralesional Bee venom vs Candida antigen in the treatment of common warts.

This study included 28 patients divided into two groups: Bee venom and Candida antigen groups, each group contains 14 patients. Each patient treated maximum for 5 sessions for 5 weeks or less if complete recovery occur.

In the current work, we decided to use a pre-sensitization skin test for bee venom because of the possible incidence of allergy against bee venom components nd to avoid hypersensitivity reactions .On the other hand, we did not make a pre-sensitization skin test for candida antigen because of the high incidence of Candia infection in our community makes the sensitivity to the injected Candida antigen highly expected.

The results of the present study demonstrated a higher efficacy, though statistically insignificant, of Bee venom in the treatment of common wart (50%) than Candida antigen (35.7%).

Collectively, the study revealed complete clearance of warts in 50% of patients treated with bee venom, while partial response was reported in the other 50% of patients and no response in 0% of patients with no recurrence in the 6-month follow-up period.

As regards isolated Candida antigen injection group, complete response was achieved in 35.7% of the studied patients, while partial response was reported in the other 64.3% of patients and no response in 0% of patients with no recurrence in the 6- month follow-up period. This rate of success was lower than that reported by Clifton et al., 2003 (47%), Alikhan et al., 2015 (39%) and Nofal et al.,2017 (61.1%), but it was higher than reported by Nofel et al., 2018 (33.3%).

Factors which may explain the different response to candida antigen in the present study as compared to other studies, the differences in the studied population selected for treatment, the number of the studied patients, the sensitivity degree to the injected antigen, and the number, type, duration and resistance of warts may be responsible for the difference between the results of our study and other related studies on Candida antigen.

To the best of our knowledge, it is the first controlled trial for treatment of warts with the intralesional Bee venom injection. Bee venom has recently been proven to be safe and can be used therapeutically in a specified dose Moga, et al., 2018 Melittin, which is a main component of Bee venom, has been reported to inhibit the replication of a number of viruses including murine retrovirus and herpes simplex virus Baghian et al., 1997 Also, . Wachinger et al., 1998.studied the inhibitory effects of melittin on HIV-1 and reported that the production of infectious and cell-free virus was inhibited in a dose-dependent manner. In addition, immunomodulatory effect of bee venom was proved by Nam et al ., 2005 who demonstrated that BV enhances the Th1 cell-dominated immune response by increasing the expression of IFN-γ mRNA, without altering the Th2 cell response in both in vitro and in vivo conditions. However, much remains to be learned. During last years, application of in vitro cell culture

methods in addition to in vivo animal models has taught us surprising immunological events regarding bee venom effects at molecular and cellular levels. These findings shed the light on applying new methods for immunotherapy and allergy diagnosis.

Table1: Demographic & clinical data between the two groups

	Bee venom group (n=14)	**Candida antigen group** (n=14)	**P**
Age (years) Mean ± SD	34.36 ± 14.7	33.36 ± 14.37	.81
Female, n (%)	12 (85.7)	10 (71.4)	.36
Duration (months) Median (Range)	18 (3 – 50)	17 (3 – 32)	.69
Previous therapy, n (%)	11 (78.6)	11 (78.6)	1

Table 2: Clinical data of the warts between the two groups.

Variable		**Bee venom group** (n=14)	**Candida antigen group** (n=14)	**P**
Warts site n (%)	Dorsum of Rt hand	5 (35.7)	3 (21.4)	.56
	Dorsum of Lt hand	4 (28.6)	4 (28.6)	
	Dorsum of both hand	--	1 (7.1)	
	Periungual	1 (7.1)	2 (14.3)	
	Dorsum of Rt foot	1 (7.1)	3 (21.4)	
	Dorsum of Lt foot	2 (14.3)	1 (7.1)	
	Left forearm	1 (7.1)	--	
Total number of Warts Median **(**Range)		2 (1 – 6)	2 (1 – 6)	.49
Recalcitrant, n (%)		4 (28.6)	6 (42.9)	.43
Warts size n (%)	< 1 cm	1 (1.7)	2 (14.3)	.54
	> 1 cm	13 (92.9)	12 (85.7)	

Table 3:Therapeutic response between the two groups

Response		**Bee venom group** (n=14)	**Candida antigen group** (n=14)	**p**
1st Session n (%)	No response	2 (14.3)	3 (21.4)	.62
	Partial response	12 (85.7)	11 (78.6)	
2nd Session n (%)	Partial response	14 (100)	14 (100)	1
	Complete response	---	---	
3rd Session n (%)	Partial response	12 (85.7)	14 (100)	.14
	Complete response	2 (14.3)	---	
Response		(total n = 12)	(total n = 14)	
4th Session n (%)	Partial response	10 (83.3)	12 (85.7)	.87
	Complete response	2 (16.7)	2 (14.3)	
Response		(total n = 10)	(total n = 12)	
5th Session n (%)	Partial response	5 (50)	9 (75)	.23
	Complete response	5 (50)	3 (25)	
Final results	No response	---	---	.45
	Partial response	7 (50)	9 (64.3)	
	Complete response	7 (50)	5 (35.7)	

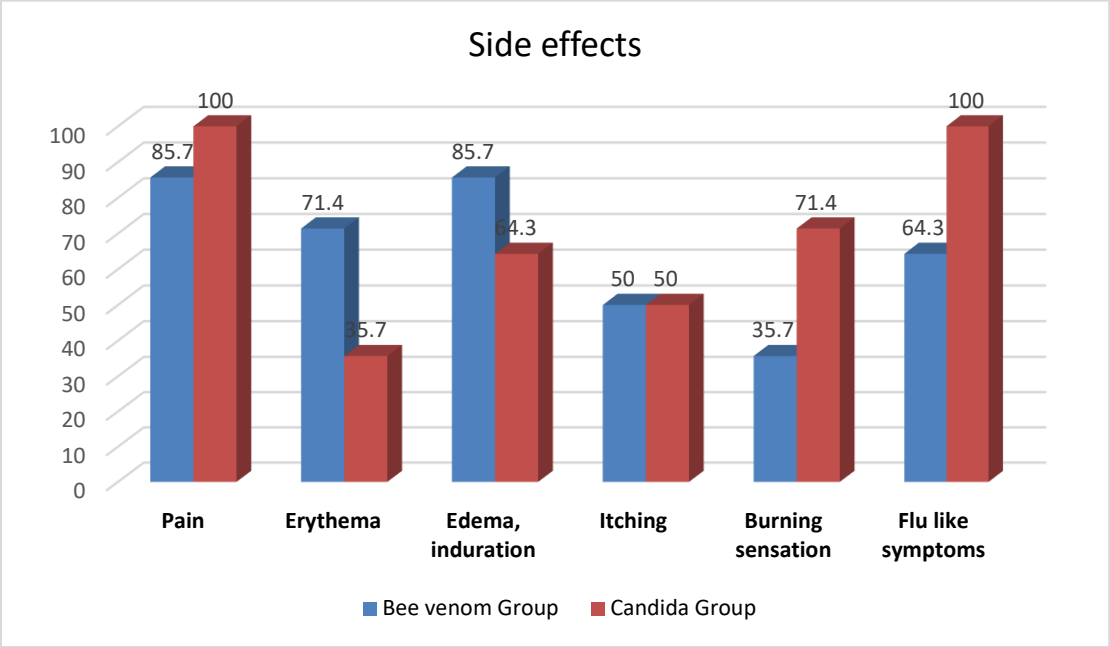
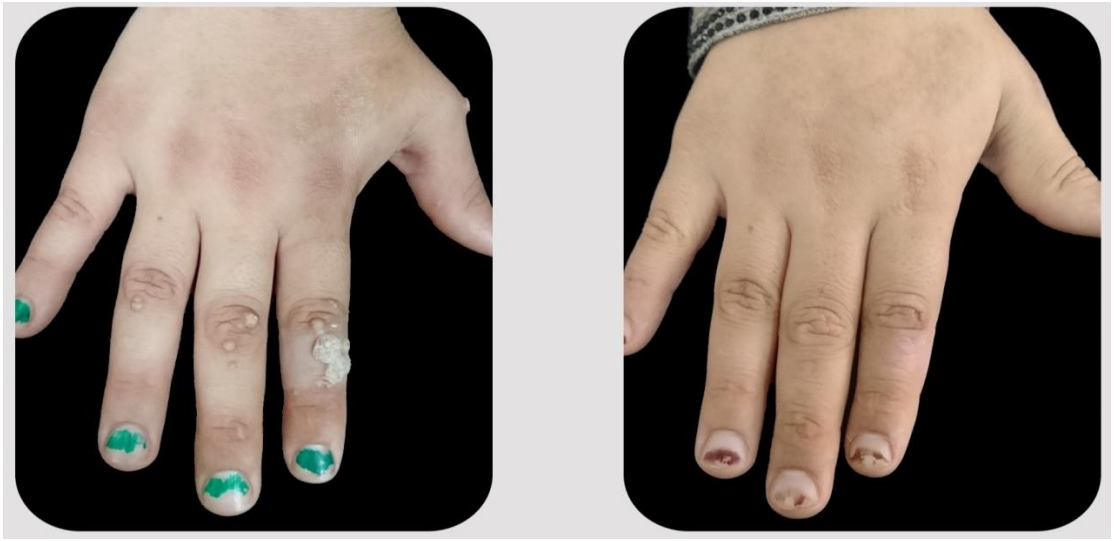
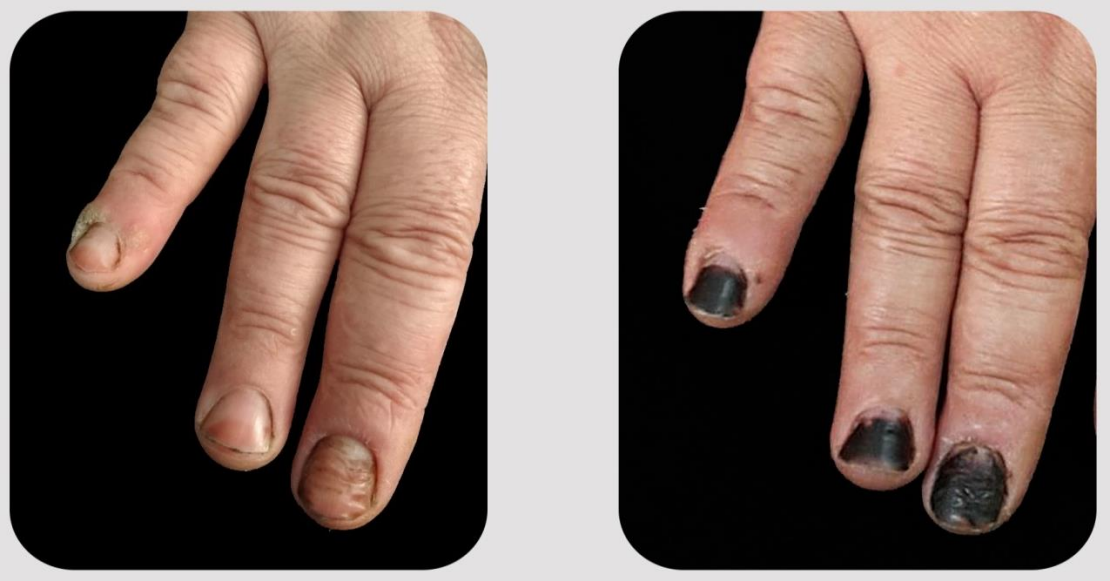


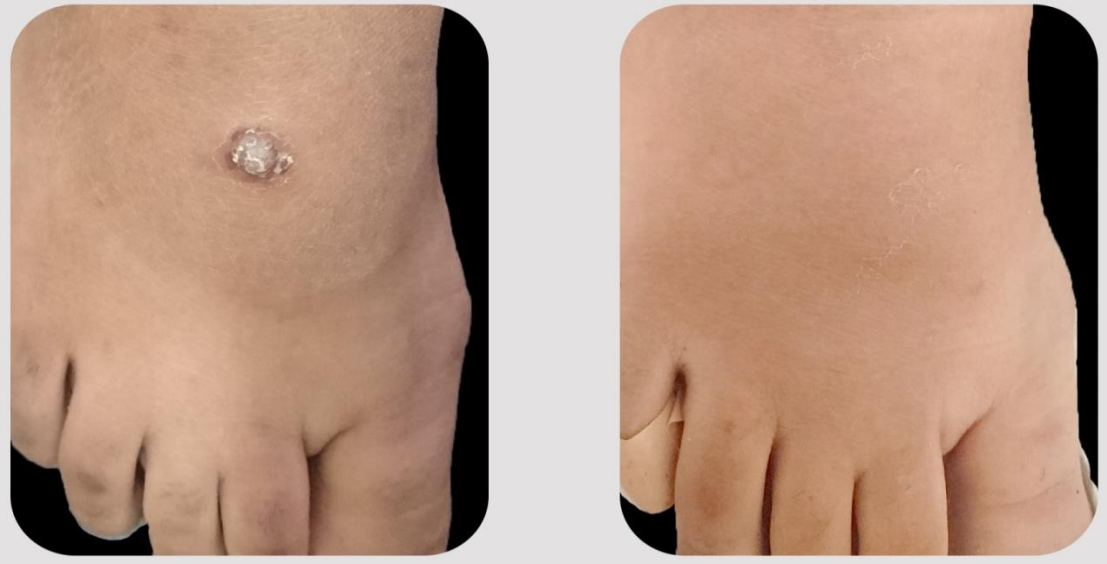
Figure 1: Side effects percentage between the two groups.



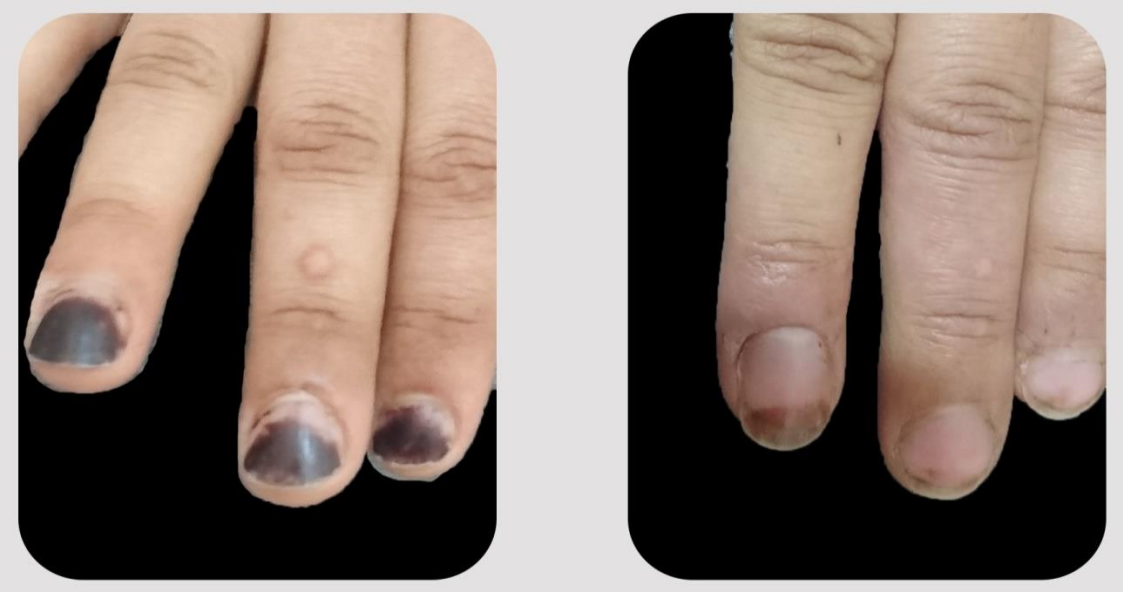
Case 1. Complete response of multiple common warts after 4 sessions of intralesional bee venom injection.



Case 2: Partial response of periungual common wart after 5 sessions of intralesional bee venom injection.



Case 3:Complete response of common wart after 5 sessions of intralesional candida antigen injection.



Case 4:Partial response of common wart after 5 sessions of intralesional candida antigen injection.

There are some aspects of immunologic interactions of bee venom components with immune cells remaining to be discovered **Oršolić,** 2012

Therefore, in our study, we depend on the antiviral, immunomodulatory and antiproliferative effect of bee venom, which are important advantages, but treatment with bee venom still needs more studies and investigations to determine the accurate dose for each virus and the definite mechanism of action of bee venom as an antiviral.

In this study, no statistically significant relationship was found between the therapeutic response to both bee venom injection and candida antigen injection, and the different clinical variables, including age, sex, site, type, size or previous therapy of warts, but a significant inverse relationship was found between the therapeutic response and disease duration (the shorter the duration of warts, the higher the response). This finding may be attributed to the higher viral load expected to increase with the longer duration of the warts.

This study revealed clearance of untreated warts, including the nearby and distant lesions. This observation comes in agreement with those reported by other studies utilizing intralesional antigen injection for the treatment of warts Phillips et al. , 2000) and King et al .,2005) This strongly indicates the development of a widespread cell-mediated immunity against HPV as a response to either bee venom or candida antigen injection; an observation that represents a great advantage of Bee venom and Candida antigens over traditional therapies.

Concerning Bee venom, we noticed that the side effects such as erythema, edema, flu like symptoms and itching fade gradually along the sessions. This observation may be due to the hypo-sensitization which occur because of repeated exposure to bee venom and this is an important aim of Bee venom immunotherapy to reduce allergic reactions occurring after exposure to bee venom Maggi, 2010.

In our study, all reported side effects were mild, tolerable, and transient and did not necessitate stoppage of treatment in any of the studied patients. There was no statistically significant difference in the adverse effects between the two studied groups except a statistically significant increase in frequency of flu like symptoms was found in candida group comparing to Bee venom group.

In the present study, no recurrence was observed in any of the studied patients in both groups after the 6-month follow-up period. Similar observations of absent or low recurrence rates have also been reported by similar related studies with Candida antigen .(Maronn et al. ,2008

This finding represents an important and promising advantage of both bee venom and candida antigen immunotherapy over traditional therapies.

CONCLUSION

In conclusion, Intralesional Bee venom injection is a promising effective and safe modality for the treatment of common warts that deserves further evaluation. Bee venom is inexpensive, well tolerated and have the potential advantage of widespread and sustained effects against HPV, without the adverse effects associated with the destructive therapies.

Based on this, we recommend the use of bee venom in different forms (cream and injection) in the treatment of common warts on a much larger scale and in comparison with other therapeutic modalities in larger controlled studies to accurately define their place in the challenging field of wart therapy. We also recommend doing in vitro studies for HPV and Bee venom to learn more about its mechanism and to help in choosing the best dose to get the best results.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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