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ORIGINAL ARTICLE

The Efficacy of Diphenylcyclopropenone in Treatment of Molluscum Contagiosum

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ABSTRACT

Background: Diphenylcyclopropenone (DPCP) contact immunotherapy has been successfully utilized in various forms for treatments of recalcitrant and facial warts, molluscum contagiosum (MC) and alopecia areata. The objective was to evaluate the safety and efficacy of DPCP in the treatment of MC.

Methods: Twenty-four patients with MC were assigned to two groups: twelve patients (group A) were treated with topical application of DPCP one session per week for a maximum of 12 sessions or until clinical cure. Also, twelve patients (group B) were subjected to topical application of normal neutral saline as a control group. Follow-up was done for 3 months.

Results: In group A, eight patients (66.7%) showed complete response while four patients (33.3%) showed partial response to the topical application of DPCP after seven to twelve sessions. However, in group B, eleven patients (91.7%) showed no response and (8.3%) showed partial response. A highly significant difference was found in the clinical response between both groups ($p<0.05$). Adverse effects were minimal and well tolerated in both groups.

Conclusion: Diphenylcyclopropenone is safe and effective therapeutic option in treatment of MC and cost effective.

Keywords: Molluscumcontagiosum; Diphenylcyclopropenone; immunotherapy

INTRODUCTION

Molluscum Contagiosum (MC) is a typical cutaneous and mucocutaneous viral disease which is particularly affecting children, youngsters, and immunocompromised persons in different ages. The infection is caused by the molluscum contagiosum virus (MCV [1]. The disease may spread by skin contact directly or by autoinoculation. Clinically, it is described by single or various umbilicated, 2 to 8 mm smooth, dome-shaped, glistening-white or ruddy papules [2]. The lesions are also described by a dominant lump, which encloses the viral particles and dead skin cells, making it exceptionally infectious. Similarly, as with different cutaneous viral contaminations, the cell mediated immunity act a significant role in resolution of this viral infection [3]. Different treatments have been submitted to speed clearance of MC in children with bothersome symptoms. These include curettage, cryotherapy, laser, and different topical agents such as tretinoin, imiquimod, and potassium hydroxide (KOH) [4]. There are several immunomodulators such as interferon α, diphenylcyclopropenone (DPCP), and cidofovir are also recommended particularly in immunodeficient patients. However, most of these methods are not tolerated by children and show an unsatisfactory response in patients with numerous lesions. Therapeutic options for MC need topical applications or damage of all lesions, frequently traumatic for kids and troublesome in patients with various lesions [5].The benefits of immunotherapy in treatment of MC contain the initiation of an MCV-concentrating memory immune response, the possible to persuade a widespread reaction with treatment of simply inaccessible lesions, 1 to 2 MC papules, absence of side effects for instance scarring, and the possible of resolution of unprocessed lesions at structurally remote locations. Furthermore, reappearance of lesions might be lesser with immunotherapy [6]. Diphenylcyclopropenone is a topically directed medication planned for treating alopecia totalis and alopecia areata. DPCP is also a harmless, active viable treatment methodology of intractable warts [7]. Diphenylcyclopropenone was first synthesized in 1959 as a powerful contact allergen in people and creatures. Ultra violet radiation and warmth prompt corruption to DPCP. Concentrations of DPCP are advertised in darker UV-murky

containers to be put away at temperature of the room. [8]. It is non-mutagenic at dilutions of fifty and one hundred mg/ml and it does not seem to have important systemic absorption after topical presentation. The concentration of DPCP is acclimated to provoke regional, pruritus, vesiculation and erythema [9].

METHODS

Study design: This clinical study included 24 patients with clinically proved MC carried out at Outpatient Clinics of Department of Dermatology, Venereology and Andrology, Zagazig University Hospitals during the period from March 2018 to December 2018 afterward the approval of Zagazig Institutional Review Board (ZU-IRB #4393/2018) at Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. They were divided equally into 2 groups; group A were treated with topical application of DPCP one session per week for a maximum of 12 sessions or until clinical cure and group B were subjected to topical application of normal neutral saline as a control group. Informed agreement was taken from all patients or from parents of children before the start of the study after explanation of all steps of the study to them. Patients diagnosed clinically with MC at any age or sexes were included in the study. Pregnant and lactated women were excluded from the study. Patients with MC lesions exclusively on genital area or periorbital or receiving any treatment for MC within the last month before the start of treatment were excluded from the study. If they were incapable to come to frequent attending for repetitive treatment were also excluded. Other exclusion criteria included patients who were anergic to DPCP or suffering from acute febrile illness, Liver failure, any generalized dermatitis and exhibited active eczema at other sites.

All patients were subjected to the followings:

Complete history taking including name, age, sex, residence, and telephone number…etc. was taken from all patients. History of current dermatological disease containing onset, course, duration, location, and history of previous treatment for the disease or associated other dermatological illnesses was collected from patients. The following data were collected from patients' history of systemic diseases, drug intake, past history of preceding treatment taken for MC and family history. General examination of whole systems was done to determine any related medical situations.

Complete dermatological examination was done to examine skin for MC lesions including site, number, and duration of lesions. The diagnosis of MC was made clinically by presence of pearly white papules with central umbilication and all patients were instructed not to use any additional MC treatment during the study period. All the participants in this study were photographed before beginning of the study by OPPO F5 camera 16 mega pixels.

Preparation, sensitization test and application of DPCP

In observation of its degradation by UV radiation, it is formulated as dilutions in acetone and darker UV-murky containers (brown bottles covered with aluminum foil) to be put away at temperature of the room [9]. It is brought as a powder from Germany by sigma pharmaceuticals. Diluted solutions of DPCP were set in brown glass bottles covered with aluminum foil and stored in a refrigerator. It dissolved in acetone to produce solutions of different concentration of DPCP.

Sensitization test before starting sessions:

After the donation of informed agreement, all patients were sensitized using concentration of 1% DPCP solution in acetone in adult, and 0.5% in children. This was applied by soaked cotton ball stick to diameter area 3 cm on the innermost upper arm, and patients were directed not to disturb the site of sensitization for 48 hours after DPCP application. The site of sensitization was examined after one week, when this site showed eczematous condition, signified by local erythema and / or slight vesiculation. If severe reaction occurred, the patients were instructed to put topical steroid on it. If no response was found out, resensitization was done up to 3 times (3 applications) until a confined response happened. If no sensitization occurred, those patients were excluded from the study [10].

Start application:

Diphenylcyclopropenone was utilized later to altogether MC lesions utilizing a cotton bud, permitted to air dry, and afterward cautiously covered to prevent passive transference. Patients went to week by week schedule visits for examination and proceeding with treatment. The measurement plan was custom fitted to every person, as indicated by reaction or response.

One week afterward preliminary sensitization, a concentration of 0.0001% DPCP solution was utilized precisely to the lesions and every weak later. Dilution was continued to the degree to occur certain irritation and erythema for 24–36 hours after the application. The concentration was augmented 5–10-fold up to a upper limit of 0.1% weekly if there was no reaction [10]. The concentration of DPCP was accustomed rest on the seriousness of the inflammatory response from the preceding application. If the responses were serious enough to make bullae or acute oozing, the concentration was reduced. The concentration was raised when the response from prior application extremely weak to make desire effects [7]. Every

visit, the patient was interrogated any concerning unfavorable impacts, and the concentration of DPCP was expanded by one stage (if no reaction had been occurred), preserved consistent (if satisfactory reaction had been attained), or diminished by one stage (if extreme blistering had happened). A remedy for non-calming antihistamine was given, if necessary, to control pruritus. The accompanying stepwise dilutions were utilized: 0.001%, 0.005%, 0.01%, 0.05%, 0.1%, 0.5%, 1%. The patients were photographed at each visit and at the end of the study.

Control group (group B)

This group included 12 MC patients, who were administered a topical application of normal neutral saline one session per week for a maximum of 12 sessions or until clinical cure.

Evaluation of the clinical response

Response to treatment in both groups was evaluated by the reduction in number of lesions and comparison of photographs at every visit with the baseline photographs. Prompt and late antagonistic impacts were additionally assessed after every treatment session and at follow up period. The response was evaluated as follows; a complete response was defined as overall vanishing of the lesions and return of typical skin markings. If there is more than 50% clearance of lesions as regard number of lesions was considered a partial response. There was no response if there is less than 50% clearance of lesions.

Follow up: Follow-up was done at each visit and consistently for 3 months after stoppage of the treatment through clinic visits to detect any recurrence.

STATISTICAL ANALYSIS

The collected data were computerized and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA 2011). Qualitative data were expressed as absolute incidences (number) & relative frequencies (percentage) and quantitative data were expressed as the mean ± SD & median (minimum-maximum). Independent samples Student's t-test was utilized to compare between two groups of normally scattered variables while Mann Whitney U test was used for non- normally distributed variables. ANOVA (f) test was applied to assess more than two independent groups of ordinarily distributed variables. Percent of categorical variables were compared using Fisher's exact test or Chi-square test when applicable. Totally tests were two sided. P value of < 0.05 was considered statistically significant results (S), and P value of ≥ 0.05 was considered statistically non-significant results (NS).

RESULTS

Twenty-four patients with multiple lesions of MC were enrolled in this study. All patients completed the study. They were divided randomly into 2 groups, group A subjected to topical DPCP and group B subjected totopical normal neutral saline as a control group. Clinical data of both groups are presented in (Table 1). At the end of treatment, in group A (topical application of DPCP); 8 patients (66.7%) showed complete response, 4 patients (33.3%) had partial response to treatment (Table 2 and Figure1,2) While group B (topical application of neutral saline), only one patient (8.3%) showed partial response and 11 patients (91.7%) showed no response (Table 2). Concerning the clinical response, there was statistically significant difference between both groups (Table 2).

Adverse effects

The adverse effects were well tolerated by most of patients. In group A, showed post treatment hyperpigmentation in 3 cases (25%), hypopigmentation in 2 cases (16.7%), pruritus in 3 cases (25%), blistering in 4 cases (33.3%) (Table3). While group B, none of patients suffered from any side effects. There was a statistically significant difference between the two groups as regards to side effects.

Recurrence

After a 3-month follow-up period, no recurrence was reported in patients of group A (Table 4).

(Table 1) Demographic data of the two studied groups:

Items	Studied groups		Test of sig.	p
	Group A (DPCP) (n=12)	Group B (Control) (n=12)		
Age (year)				
Mean ±SD	5.5±2.32	4.5±1.39	MW	0.26
Median	5	5		(NS)
Sex				
Girl	7 (58%)	9 (75%)	F	0.66
Boy	5 (42%)	3 (25%)		(NS)
Disease duration (month) :				
Mean ±SD				

Items	Studied groups		Test of sig.	p
	Group A (DPCP) (n=12)	Group B (Control) (n=12)		
(min-max)	3.5±1.8 (1-6)	3.4± 2.2 (1 – 8)	MW	0.77 (NS)
Site of lesion no (%): **one site** **multiple site**	 2(16.7%) 10(83.3%)	 4(33.3%) 8(66.7%)	 F	 0.6 (NS)
Number of lesion: **Mean ±SD** **(min-max)** **≤3** **≥4**	 13±11 (3-35) 3(25%) 9(75%)	 20±33 (1-121) 2(16.7) 10(83.3)	 MW MW	 0.93 (NS)
Previous treatment **No** **Yes** **Type of previous treatment** **Cryocautery** **Electrocautery** **KOH** **Topical tretinoin**	 8(66.7%) 4(33.4%) 1(8.3%) 1(8.3%) 1(8.3%) 1(8.3%)	 9(75%) 3(25%) 0 (0%) 2(16.7%) 0 (0%) 1(8.3%)		 0.99
MW= Mann-Whitney U F= fisher exact				

Table (2): Clinical response, treatment sessions, duration and recurrence among the studied groups:

Items	Studied groups		Test of sig (t)	p
	Group A (DPCP) (n=12) No (%)	Group B (Control) (n=12) No (%)		
Number of session: **Mean ±SD** **median(min-max)**	9.7±2.2 10(7-12)	5.4±1 8(6-10)	7.4	0.0001
Duration of treatment (weeks) **Mean ±SD** **median(min-max)**	9.7±2.2 10(7-12)	5.4±1 8(6-10)	7.4	0.0001
Response: **Complete** **Partial** **No response**	 8(66.7) 4(33.3) 0 (0)	 0 (0) 1 (8.3) 11(91.7)	 X^2=11.50	 0.007
X^2= Chi square test				

Table (3): Adverse effects of the treatment with DPCP

Adverse effects of treatment		Group A (DPCP) (n=12) No (%)
Hypopigmentation	**present**	2(16.7)
	Absent	10(83.3)
Pruritus	**present**	

Adverse effects of treatment		Group A (DPCP) (n=12) No (%)
		3(25)
	Absent	9(75)
Hyperpigmentation	present	3(25)
	Absent	9(75)
Blistering	present	4(33.3)
	Absent	8(66.7)
Erythema and edema	present	0
	Absent	12(100)

Table (4): Recurrence of lesions in patients with complete response after therapy

Item	Studied groups Group A(DPCP) No (%)
Recurrence	
No	12(100)
Yes	0 (0)
DPCP: Diphenylcyclopropenone	

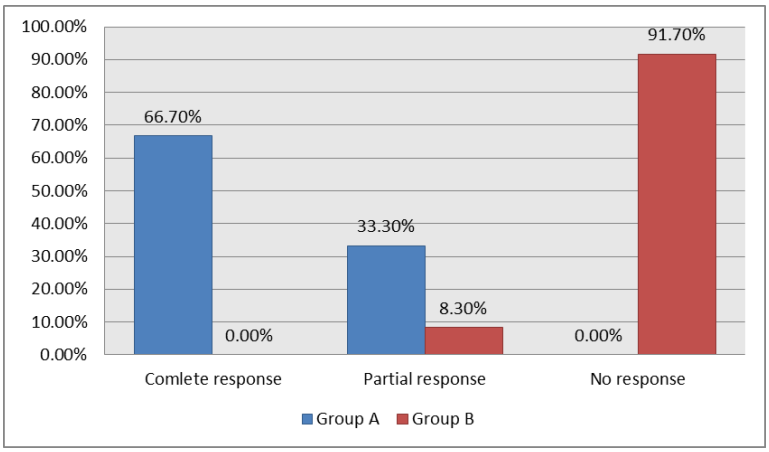

Figure (1): Bar chart showing the percent of clinical response among the studied groups.

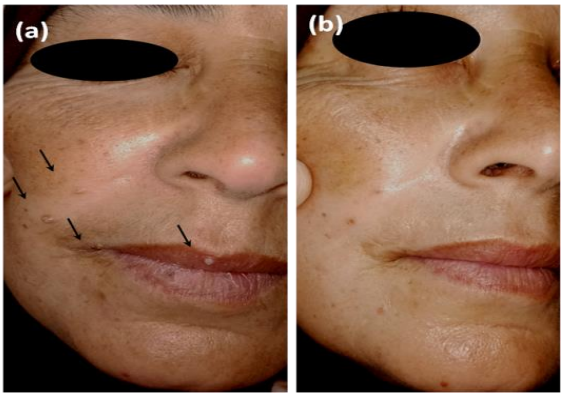

Figure (2): (a) Female patient, aged 50 years old female with MC on the right side of the face, before the treatment of Diphenylcyclopropenone (DPCP), (b) the same patient after the treatment showing complete response to DPCP after the 12th session.

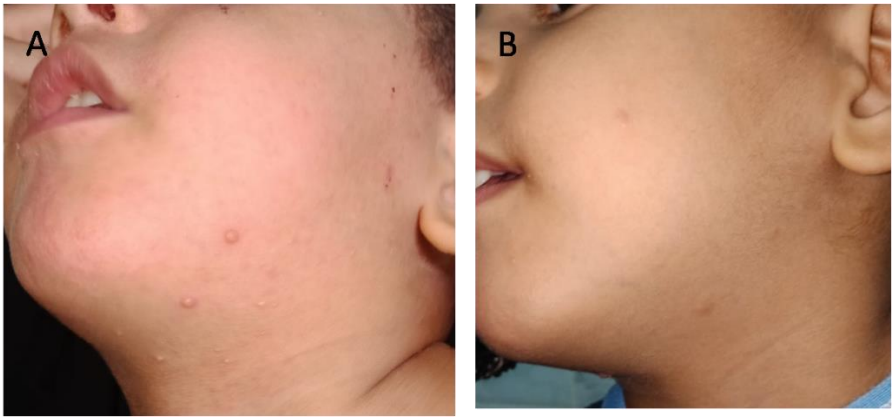

Figure (3): (a) A boy, aged 4 years old with MC on face and neck, before the treatment of Diphenylcyclopropenone (DPCP), (b) the same patient after the treatment showing complete response to DPCP after the 12th session.

DISCUSSION

Molluscum contagiosum is a typical skin contamination that is caused by a poxvirus and happens generally in kids. Its resolutions occur within few months in people without immune deficiency [11]. It is most easily transmitted by direct skin-to-skin contact or mucous membranes. It can arise in the genital area from sexual contact and may also spread by shaving and scratching. Clinically, it is characterized by one or more smooth, vault-shaped, glistening-white or ruddy papules with innermost unbilication [12].

Molluscum contagiosum is mostly a benign and self-limited infection. The common suggestion for treatment is hopeful administration by means of impulsive resolve that occur commonly after several months. The cell mediated immunity act a significant role in the disease resolution. Treatment may be preferred for public or cosmetic reasons or to prevent dissemination of this infection [13]. There are several treatment approaches; destructive, immunologic, chemicals and antiviral. No single intervention is effective and suitable to all patients with MC. The treatment variety is prescribed corresponding to status of immunity in patients [14]. Selection of the most appropriate means of treatment is usually difficult because of the availability of various therapeutic lines and the immune status of the patients. The treatment options will be determined by age of the patient, number and location of the lesions [15]. Cell-mediated immunity act a significant role in the pathogenesis of MC, Immunotherapy has the preferred standpoint over conventional medications in that it improves the virus recognition by means of the immune system; this permits clearance of the cured lesions and others at remote anatomical sites [16].

Diphenycyclopropenone acts as a topical immunosensitizer. In this work, we aimed to evaluate the safety and efficacy of DPCP in treatment of MC. To our knowledge, no previous published data using DPCP in a case- controlled study.

In this study, 24 patients with MC were designed equally to 2 groups. Group A received DPCP and group B was the control group (placebo). The demographic and clinical data were presented in (Table1). No significant deference was found between both groups regarding age, sex, duration or number of lesions (table1). At the end of the treatment, in group B eight patients (66.7%) showed complete response after seven to twelve sessions and four patients (33.3%) showed partial response with overall response rate of 100%. There was a highly significant difference between the two groups (P=0.007) (Table2). No recurrence was reported in the three months follow up period in all patients showed complete response in this group therapy of DPCP (Table4).

Our results seem to be comparable to that reported by Kang et al [10] of a full remission in 14 out of the 22 (63.6%) patients treated with DPCP. Partial clearance of lesions was detected in 3 patients (13.6%). On thecontrary Kim et al [17] also reportedthat complete cure in 12 out of 23 (52.2%) patients treated with DPCP, while 11 patients (47.8%) showed treatment failure.

In our study the adverse effects were tolerated by most of patients. The potential adverse effects were not inconsiderable. Unprepossessing pigmentation at the site of sensitization happens in few patients and therefore sensitization is best done on the innermost side of upper arm. Post treatment pigmentation changes were most common, either hyperpigmentation (25%) or hypopigmentation (16.7%). Blistering at the site of treatment or sensitization was commonly occurred all through treatment (33.3%). Pruritus also occurred in 25% of cases.

In contrast to our results of adverse effects, Kang et al [10] reported that 4 patients dropped out as a

consequence of the side effects of the treatment despite of mild pruritus and partial erythema. But in Kim et al [14] side effects were mild and no patients dropped out of the study. Mild side effects occurred such as erythema in 8 patients (34.8%), pruritus in 6 patients (26.1%) and vesicle in 2 patients (8.7%).

We assumed that the earlier the sensitization occurs, the more effective DPCP immunotherapy may be. This can be confirmed with the number of treatment sessions that ranged from 7 to 12 sessions.

DPCP had demonstrated a promising efficacy in treatment of MC in individual case reports. It wasreported a case of 3 years old child with multiple lesions of MC on the penoscrotal area, extremities and trunk of 7 months duration treated with DPCP. All of the lesions cleared after 8 weeks of treatment [18]. Chularojanamontri et al [19] also reported a case of generalized molluscum contagiosum in an HIV patient cured with DPCP with minimal and transient side effects. However, DPCP has not been generally used in immunocompromised patients; this report demonstrated a great success of treatment in a patient of HIV. Diphenylcyclopropenone is a contact immunotherapy. It acts on induction of the delayed-type hypersensitivity. It is a universal contact sensitizer in which the response to treatment can occur in remote areas other than those of topical application. The mechanism of action of DPCP has been less comprehensively reconnoitered. There are several theories contain alterations in levels of cytokine, general inflammation leading to recession of lesions, persuading a specific immune reaction. DPCP prompts a reversal of the CD4: CD8 ratio such that CD8 cells preponderate in a dense epidermal and dermal inflammatory infiltrate. Some studies reported successful treatment in primary and secondary malignant melanoma [20]. Topical immunotherapy using DPCP is cheap and reasonably non-aggressive mehod and had better be considered in patients with nearby progressive skin metastases that are inappropriate for other treatments [19]. Topical DPCP therapy can be considered an excellent select as a principal route in treatment, with a widespread therapy expected in furthermost patients who possess several lesions and can undertake uninterrupted treatment throughout regular hospital visits [10].

CONCLUSION

In conclusion, topical immunotherapy with DPCP seems to be less expensive, generally well accepted by patients, more effective and safer treatment option particularly for generalized non-genital MC lesions and uncooperative patients.

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