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Comparative Study between the Efficacy of Intralesional Injection of Platelet Rich Plasma versus Topical Zink Oxide Paste 20% in the Treatment of Common Warts

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ABSTRACT

Background: Cutaneous warts are benign epidermal proliferations caused by human papilloma virus (HPV). Zink (Zn) has been utilized in different preparations in the treatment of common warts (CWs) as oral Zn sulphate, intralesional 2% Zn sulphate, topical application of 10%, and 5% Zn sulfate ($ZnSO_4$) with different success rates. The platelet rich plasma (PRP) is being utilized in numerous and various dermatological indications as in alopecia, tissue regeneration, wound healing, scar revision, and skin rejuvenation.

Objective: To compare the efficacy of intralesional injection (ILI) of platelet rich plasma versus 20% topical Zn oxide (ZnO) paste in treatment of common viral warts.

Patients and Methods: This study was a prospective randomized controlled trial (RCT) that was conducted over one year and included 100 patients with clinically evident, numerous CWs and were divided into two groups, group **A** comprised 50 patients treated with ILI of autologous PRP (APRP) and group **B** included 50 patients managed with 20% ZnO paste. The outcomes were assessed one month, two months and after six months from the last injection.

Results: After one month of treatment, Group A had a notably better outcome in terms of excellent responses to treatment. After six months of treatment there was a significant difference in the rate of complete cures where group A showed statistically significant higher rates of complete cure. The mean percentage of improvement for Group A was statistically significantly higher than in Group B (p value<0.001).

Conclusion: PRP was superior in efficacy to topically applied 20% ZnO paste in treatment of common viral warts.

Keywords: Intralesional Injection, Platelet Rich Plasma, Topical Zink Oxide Paste 20%, Warts.

INTRODUCTION

Warts are benign epidermal lesions**,** presented as smooth, flat-topped papules on the face and dorsum of hands (plane wart) or as one or more dome-shaped keratotic lesions with exophytic growth or endophytic keratotic papules on pressure points of the soles (plantar wart) [1]. There are more than 180 strains of HPV, but those most frequently responsible for warts are types 1, 2, 4, 27, 57 and 63 [2]**.**

The primary targets of HPV are basal keratinocytes, or, in other words, keratinocytes, which form the deepest layer of the epidermis and are undergoing rapid cellular divisions [3].

Zink (Zn) has been considered an essential trace element. The skin as well as its appendages is rich in Zn. From the historical point of view, application of topical Zn salts, which include ZnO or calamine, could be utilized to enhance the process of wound healing [4]. Zn has important roles in terms of the management of several dermatological disorders. Essentially, it acts as an immunomodulator agent that has anti-viral activity, and antioxidant properties [5]. In addition, it adjusts DNA-RNA related enzymes. Topical application of Zn could trigger a sequence of immunological occasions. It induces its action by causing inflammation with subsequent stimulation of T-lymphocytes, which ultimately ends in INF release that could overcome warts by macrophage stimulation [6].

A lot of studies have been carried out on wart management; however, their outcomes have to be properly evaluated owing to the considerable placebo effects [7]. In addition, PRP plays essential role in the context of treatment of many skin disorders, which include alopecia, ulcers, and acne vulgaris. Because it promotes tissue regeneration and healing, its use has been expanded to include burns, hyperpigmentation, and different skin disorders [8]**.**

Platelet rich plasma plays an essential function with regard to the bioactivation of dermal fibroblasts as it activates the coagulation cascades. Thrombin converts fibrinogen to fibrin, causing an essential clot to form in order to accomplish homeostasis and facilitating the formation of several proteins for tissue healing. As a result, tissue healing is encouraged, owing to the increase in its growth factor (GF) levels [9].

Aim of study was to compare the efficacy of ILI of PRP vs topical ZnO paste 20% in the context of CWs treatment.

PATIENTS AND METHODS

This study was a prospective RCT that was conducted over a period of one year and included 100 patients with clinically evident, numerous CWs who recruited from those attending the outpatient clinic of Dermatology, Andrology and STDs Department at Mansoura.

Patients were divided into two groups: Group A: included 50 cases treated with ILI of APRP, and **Group B:** Included 50 cases treated with 20% Zn oxide paste. We included patients from both genders aged 18-60 presented with clinically evident, numerous CWs but we excluded patients with systemic disorders and bleeding disorders, patients with chronic skin diseases

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as eczema, autoimmune disease, cold sensitivity and skin allergy, pregnancy, breastfeeding and immunosuppressed patients, smoker patients, patients with warm, or of allergic contact dermatitis (ACD) to topical Zn oxide and patients had inflamed warts which were painful, red, and swollen.

METHODS

After enrolling the patients, informed consent and photographs were taken before starting the procedure. All the participants were subjected to through history taking that comprised personal history (age, sex, residence, occupation and family history) and present history (onset, course, duration, aggravating factors and previous medication). The complete physical examination included general examination to exclude of systemic diseases and dermatologic examination for numbers, anatomical distribution, types of warts, size, activity of any new lesions, interval warts and presence of 2ry bacterial infections. Warts were diagnosed via observation of firm papules with verrucous surface.

Therapeutic plan

Group A patients were treated by ILI of APRP every month till full clearance or for a maximum of two sessions. Twenty mm of blood was withdrawn in a sterile test tube, and after that, it was sent for centrifugation at 1000 g for ten minutes to isolate both the plasma and platelets (PLT). The lower three ml of the plasma were used as PRP concentrate following centrifugation. A topical anaesthetic agent was applied to the managed area for half an hour, and after that, 0.1 ml of PRP was given by ILI. Group A patients were assessed (based on clinical assessment and photographic pictures) prior to ILI, one month following each injection, and six months from the last one. All cases were questioned to record if there were any adverse events following ILI.

Cases were assessed and categorized for improvements as, complete remission (CR), if warts totally disappeared, partial resolution, if warts fifty percent disappeared, minimal resolution, if warts less than fifty percent disappeared and no resolution, if warts weren't disappeared.

Group B patients were told to take their medication once every twelve hours. Before applying the treatment again, patients must wait fifteen min for it to dry and then massage the warts. Patients were regularly examined every month to assess number, size and to take photos to reissue the treatment, to conform appropriate application and to assess the progress. The patients were followed up for three months, or until they recovered completely, whichever happened first.

Outcomes were evaluated with regard to no response to complete cure based on the percentage of decrease in number of warts from the initial examination and was graded as [10], grade zero demonstrated no response, grade I showed mild response (1-25%), grade II showed moderate response (26-50%), grade III demonstrated considerable response (51-75%), grade IV demonstrated excellent response (76-99%) and grade 5 demonstrated complete cure (100%).

Ethical approval:

Mansoura Medical Ethics Committee of the Mansoura Faculty of Medicine approved this study. After obtaining the necessary information, all participants provided signed consent. The Helsinki Declaration was observed throughout the study's duration.

Statistical analysis

The collected data were coded, and analyzed by utilizing SPSS. Mean±SD were utilized for numerical data. Frequency and percentage were utilized for non-numerical data. Student T Test was utilized to evaluate the significant difference between the two studied groups regarding parametric numerical data. Mann-Whitney U test was utilized to evaluate the significant difference of a non-parametric variable between the 2 studied groups. Chi-Square test was utilized to assess the correlation between 2 qualitative variables. Univariate and multivariate logistic regression analysis were used to calculate odds ratio (OR), which was used to assess the degree of relationship between an exposure and an outcome. In terms of all the previously utilized tests, p was considered significant when its value was less than 0.05.

RESULTS

This study comprised 100 patients divided into to 2 groups; group **A** comprised 50 patients treated with ILI of APRP and group **B** comprised 50 patients treated with 20% Zn oxide paste. Table **(1)** displays no significant difference between both groups concerning demographic data and number of lesions, while size of lesions showed statistically significant differences between both groups as group B showed large lesions.

Table (1): Demographic data among studied groups, number and size of lesions

		Group A	Group B	p
		n=50	n=50	
Age (years)	**Mean±SD**	30.9±10.3	31±8.3	0.823
Gender	**Female**	34(68%)	31(62%)	0.529
	Male	16(32%)	19(38%)	
Mean number of lesions	**Mean±SD**	3.6±1.5	4±2	0.415
Number of lesions	**1**	4(8%)	4(8%)	1.000
	2-5	39(78%)	35(70%)	0.346
	>5	7(14%)	11(22%)	0.642
Size of lesion (mm)	**Mean±SD**	4±2.9	7.3±3.9	<0.001*

*: Significant

Table **(2)** shows that there was no significant difference between both groups regarding the morphological types of the studied warts.

Table (2): Morphological type among studied groups

Morphological type	Group A	Group B	p
	n=50	n=50	
Common Wart	19(38%)	19(38%)	1.000
Filiform Wart	3(6%)	3(6%)	1.000
Mosaic Wart	4(8%)	7(14%)	0.338
Plane Wart	6(12%)	5(10%)	0.749
Plantar Wart	3(6%)	0(0%)	0.079
Planter Wart	15(30%)	16(32%)	0.829

Table **(3)** shows the scoring before treatment for studied groups. According to the data, all participants in both groups (100% in group A and 100% in group B) were classified under "No response" before the initiation of treatment. Regarding the outcomes of follow-up scores after 1 month of treatment for studied groups, Group A had a notably better significant outcome in terms of excellent responses to treatment. Group B had a significant higher rate of moderate responses in comparison to group A after 2 months. There was much higher significant rate of significant responses in group B compared to group A after 6 months. There was a statistically significant greater rate of complete cure in group A.

Table (3): Scoring before and after treatment among studied groups.

		Group A	Group B	p
		n=50	n=50	
Scoring before treatment	**No response**	50(100%)	50(100%)	1.000
Follow Up (Score) after 1 month	**No response**	4(8%)	3(6%)	0.695
	Mild response	4(8%)	9(18%)	0.137
	Moderate response	7(14%)	14(28%)	0.086
	Significant response	13(26%)	14(28%)	0.822
	Excellent response	21(42%)	7(14%)	0.002*
	Complete cure	1(2%)	3(6%)	0.307
Follow Up (Score) after 2 months	**No response**	0(0%)	3(6%)	0.079
	Mild response	4(8%)	1(2%)	0.169
	Moderate response	4(8%)	13(26%)	0.017*
	Significant response	9(18%)	12(24%)	0.461
	Excellent response	18(36%)	14(28%)	0.391
	Complete cure	15(30%)	7(14%)	0.053
Follow Up (Score) after 6 months	**No response**	0(0%)	3(6%)	0.079
	Mild response	1(2%)	0(0%)	0.315
	Moderate response	5(10%)	6(12%)	0.749
	Significant response	2(4%)	14(28%)	0.001*
	Excellent response	15(30%)	15(30%)	1.000
	Complete cure	27(54%)	12(24%)	0.002*

*: Significant

The mean percentage of improvement for group A was significantly higher than group B (Table 4).

Table (4): Percentage of improvement in response score before and after treatment

		Group A	**Group B**	**p**
		n=50	n=50	
Percentage of improvement	**Mean±SD**	87.2±21.7	72.8±27.3	<0.001*

*: Significant

Age showed a statistically insignificant correlation with treatment improvement. In contrast, a significant negative correlation between improvement in treatment response and number of lesions, duration of lesions and size of lesions was found (Table 5).

Table (5): Correlation between percentage of improvement in response to treatment and other studied parameters

	r	**p**
Age	-0.072	0.477
Number of lesions	-0.241	0.016*
Duration of lesions	-0.335	<0.001*
Size of lesions	-0.182	0.07*

*: Significant.

Table **(6)** shows the logistic regression analysis for factors associated with a low response to treatment among studied cases, with utilizing both univariate and multivariate approaches to identify significant predictors. In the univariate analysis, treatment with Zn oxide and the large size of lesions were statistically significant factors. In the multivariate analysis, which adjusts for multiple factors simultaneously, treatment with Zn oxide remained significant. Other factors such as age, gender, high number of lesions, long duration of lesions, and new lesions did not show significant associations with treatment response in either univariate or multivariate analysis.

Table (6): Logistic regression of factors accompanied by low response among studied cases

	Univariate			***Multivariate***		
	p	***OR***	***CI***	***p***	***OR***	***CI***
Treatment with Zn oxide	0.002*	4.472	1.749 - 11.433	0.03*	2.434	1.943 – 6.983
Age	0.427	1.019	0.973 - 1.066	-	-	-
Gender	0.403	0.677	0.271 - 1.69	-	-	-
High number of lesions	0.429	1.102	0.866 - 1.401	-	-	-
Large size of lesion	0.04*	1.379	1.178 - 1.614	0.365	1.493	1.294 – 1.453
Long duration of lesions	0.474	0.983	0.937 - 1.031	-	-	-
New lesions	0.610	0.853	0.463 - 1.572	-	-	-

*: Significant.

DISCUSSION

CWs are epidermal lesions caused by HPV infection of keratinocytes [11]. HPV is a dsDNA virus with more than two hundred forms being recognized [12]. Of note, HPV life cycle is accompanied by epithelial proliferation and differentiation [13]. Cutaneous HPV infection frequently presents as warts [14].

Most of treatment modalities for warts depend mainly on ablation of the infected tissue [15]. In spite of different treatment modalities, none of such medications has antiviral action [16]. Zn has been considered as an immunomodulating drug in the context of wart management and adjusts DNA-RNA related enzymes [17]. Topical Zn could trigger a sequence of immunological occasions. It has the ability to induce inflammation with subsequent activation of T-lymphocytes, which ultimately ends in INF discharge, as a result leading to action of macrophages against wart-derived keratinocytes [18]. ILI of PRP in plantar warts could be efficient and safe immunotherapy; this could be clarified by the fact that PLT express a lot of TLRs 1, 2, 3, 4, 6, 7, and 9 [19]. Upon stimulation, the TLRs increase the synthesis of INF and several cytokines as IL-6, IL-8 and TNF-α, which after that trigger several immune cells with subsequent increase in the inflammatory process [20].

Thus, we aimed to compare the efficacy of ILI of PRP vs 20% topical ZnO paste in treatment of CWs. The current study was conducted on a total of 100 cases with clinically evident, numerous common warts. They were divided into two groups, group A comprised 50 cases treated with ILI of APRP and group B comprised 50 cases treated with 20% ZnO paste. In the present study, after one month of treatment both groups showed a minimal insignificant difference in lack of response to treatment, with 8% in Group A and 6% in Group B. Group A had a notably better outcome in terms of excellent responses to treatment.

In the present study, after two months of treatment the complete cure rates were 30% for group A and 14%

for group B, with a p-value suggesting a trend towards significance but not conclusively different. After six months of treatment both groups reported the same 30% excellent response rate. There was a significant difference in the rate of complete cures, with 54% in group A and only 24% in group B. Our study revealed that, the mean percentage of improvement for group A was reported as 87.2% with a standard deviation of 21.7, whereas for group B, it was slightly lower at 72.8% with a standard deviation of 27.3. Statistical test was applied to assess the difference between the two groups, resulting in a significant p-value of less than 0.001. So, group A who was treated with ILI of PRP has higher response rate than group B who was treated with topical 20% Zn oxide paste.

In line with our results **Arshad *et al*.** [18] found out that the therapeutic outcomes of 20% topical ZnO of cutaneous warts of hands and feet, 49.8% patients had CR at the termination of three months of therapy [6].

Khattar *et al*. [6] compared the efficiency of topical ZnO and combined salicylic acid and lactic acid with regard to wart management. In terms of ZnO group, fifty percent achieved CR (grade V), one (6.25%) revealed 75% response (grade III), four (25%) revealed 50% response (grade II), whereas three (18.75%) revealed no improvement (grade zero). Fifty percent of the cases demonstrated full cure in ZnO group, in comparison to forty two percent in combined group.

On the other hand, **Niazi** [7] study displayed that combined 15% salicylic acid and 15% is of great efficiency compared to 20% ZnO ointment in terms of management of CWs. This came in the same line with Cochrane review on local wart management [21]. Discrepancies from the aforementioned research could be owing to the large sample size; and only cases with CWs were included in **Niazi** [7] research.

Regarding the use of PRP therapy in warts, **Abu El-Hamd and Aboeldahab** [20] assessed the potential efficiency of PRP in the management of multiple resistant plane warts. CR was noticed in 20% after the 1st session and 100% after the 2nd session. Following a period of six months of follow-up from the last session, no relapse was recorded. So, they considered ILI of PRP in the plane warts as efficient and safe immunotherapy; this might be clarified by PLT expression of TLRs 1-4, 6, 7, and 9 [19].

Abu El-Hamd and **Aboeldahab** [20] recorded that there was a CR for recalcitrant plantar warts of an immunocompetent male cases following three sessions of ILI of APRP (30 days apart), combined with topical salicylic acid 30% solution (every 12 hours). Additionally, there was no relapse following a 9-month follow-up. No noticeable adverse events were recorded.

The advantage of Zn use in warts and different infectious disorders are broadly recorded, however the mechanism of Zn modifying immune responses and fight against certain viruses is still unexplained. Six studies assessed the efficiency of oral $ZnSO_4$ as a single agent on resistant multiple warts. The majority of them reported that oral intake of Zn was an effective therapy, and three studies demonstrated that Zn values in cases were significantly lower compared to matched age and sex healthy controls. A lot of observational studies demonstrated that serum Zn value reduced in recalcitrant multiple warts cases [22-24]. As a result, Zn deficiency could be accompanied by extensive or recalcitrant warts. On the other hand, till now it isn't clear if cases with Zn deficits have a greater possibility of HPV infection; certain researches demonstrated no significant change in serum Zn value between cases with warts and apparently normal subjects (the control group) [25,26].

In fact, serum Zn value could not be used as a reliable indicator for total body Zn condition unless it is extremely low and could vary broadly. Two previous studies[27,28] revealed no response after using oral $ZnSO_4$ together with other therapies. Remarkably, it has been demonstrated that combined Zn and traditional medications seem to be superior to decreasing the risk of relapse of genital warts among females. On the other hand, there is not enough data to support the regular use of oral zinc together with traditional medications in the context of wart management [27,28].

It has been demonstrated that; some Middle East opinions reinforces the use of ILI of 2% $ZnSO_4$. They have demonstrated that; CR following injections differed from 53 to 98%. The mixed outcomes could be related to the changes of the treated warts (resistant wart or ordinary wart), the number of injected warts (single or multiple), the sample size, and the number of the therapeutic sessions. On the other hand, the side effects were considerable too, which might relatively restrict its use. Due to these discrepancies between results, further RCTs have to be conducted in the future to prove or disprove these controversies [29].

In the current study, age shows a statistically insignificant correlation with treatment improvement. In contrast, a significant negative correlation was found between improvement in treatment response and number of lesions, duration of lesions and size of lesions.

Khattar *et al.* [6] revealed that age had a significant impact on treatment. They have demonstrated that the therapeutic effects on time to cure was comparable in the two studied groups.

CONCLUSIONS

We concluded that PRP was superior in efficacy to topically applied 20% ZnO paste in the context of CW managemant. It could be used as a possible alternative for cases not responding to conventional approaches.

RECOMMENDATIONS

More sessions of treatment are recommended and a maintenance therapy in the form of one session every 3 months to avoid recurrence may be valuable. Further studies with, longer duration of treatment, are recommended for better evaluation of long-term effect

of the treatment. Additional studies have to be conducted in the future to detect the safety and appropriate concentration of ILI and to assess the effecincy of oral and topical ZnO in the context of wart managemant. In addition, RCTs have to be conducted to assess PRP effecincy in terms of the management of various forms of wart.

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