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ORIGINAL ARTICLE

A double-blind, randomized controlled trial on the efficacy and safety of intralesional 2% zinc sulfate in the treatment of verruca vulgaris in a tertiary hospital

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ABSTRACT

BACKGROUND Verruca vulgaris ranked 10th in the top 10 diseases in 2019 seen among the Philippine Dermatological Society training institutions. The efficacy of immunotherapy, such as intralesional zinc sulfate (ZS), for warts were reported. Considering the limited studies with promising results on verruca, a study on the efficacy and safety of intralesional zinc in the treatment of verruca was considered.

OBJECTIVE This study aims to determine the efficacy and safety of intralesional 2% ZS in comparison to intralesional purified protein derivative (PPD) among adult patients with verruca vulgaris.

METHODS This is a double-blind, randomized, controlled trial involving 44 patients allocated to group ZS (n=22) and PPD (n=22). Intralesional injections of ZS or PPD to the largest wart were done at weeks 0, 2, 4, 6, 8, 10. Clearance and size reduction of the target and distant wart at 12th week and recurrence at 14th week were assessed. Adverse effects were checked.

RESULTS At the 12th week of treatment, higher proportion in group ZS patients achieved total resolution of the target lesion compared to PPD, but results were not statistically significant (29% vs. 19%). Both groups showed decline in the target lesion size. The median size reduction between the two groups showed no significant differences. Three patients from group ZS showed clearance of distant warts while none in group PPD. There was no recurrence of all previously resolved warts. Adverse reactions were pain, edema, and erythema.

CONCLUSION Intralesional 2% zinc sulfate (29%) was efficacious and safe compared to Intralesional PPD (19%) but the difference was not statistically significant. There was clearance of distant warts in 5% of group ZS patients. The mild adverse events did not warrant discontinuation of treatment.

KEYWORDS intralesional zinc sulfate, intralesional purified protein derivative, verruca vulgaris

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INTRODUCTION

Verruca vulgaris, caused by human papilloma virus (HPV), is a common skin condition worldwide which may be transmitted through breaks in the skin or autoinoculation into adjacent skin. It ranked 10th in the top 10 diseases in 2019 seen among the training institutions of the Philippine Dermatological Society with a prevalence rate of 2.2%.[1] It presents as small hyperkeratotic proliferations which can spread and remain subclinical.[2] In the treatment of warts, the modality is chosen after considering the location, extent of the lesions and patient's cooperation. The treatment modalities which are currently available are topical caustics and acids, electrodessication, cryotherapy, surgical excision and immunotherapy.[2] These modalities are not consistently effective and may be cumbersome for a lot of patients.

The most common treatment for warts is physical destruction of the lesion. Treatment on numerous lesions using physical destruction, such as electrocautery, curettage, and cryotherapy is avoided by some patients due to pain, discomfort, recurrence and prolonged healing time. Moreover, the goal of physically destructive therapies is to eliminate the lesion but this does not completely eradicate the virus. Success rates of 65-85% were found with the use of electrocautery and curettage but the high recurrence rate of 30% should be considered when choosing these as treatments.[3] There were also findings of peripheral spread of virus in warts treated with electrocautery which was attributed to incomplete eradication of the virus or koebnerization.[3]

Chemical treatment for verruca consists of

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salicylic acid, trichloroacetic and monochloroacetic acid, glutaraldehyde, and cantharidin. The cure rates for salicylic acid vary between 15-49% which is low when compared to physical destruction or immunotherapy.[4] There is inadequate trial evidence of trichloroacetic acid in the treatment of verruca. Monochloroacetic acid showed a cure rate of 61%; however, it is highly corrosive and toxic.[4] Glutaraldehyde 10% paint showed a cure rate of 71% but there were reports of deep necrosis due to repeated application. Cantharidin showed good response rates in the treatment of verruca; however, it involved prolonged and

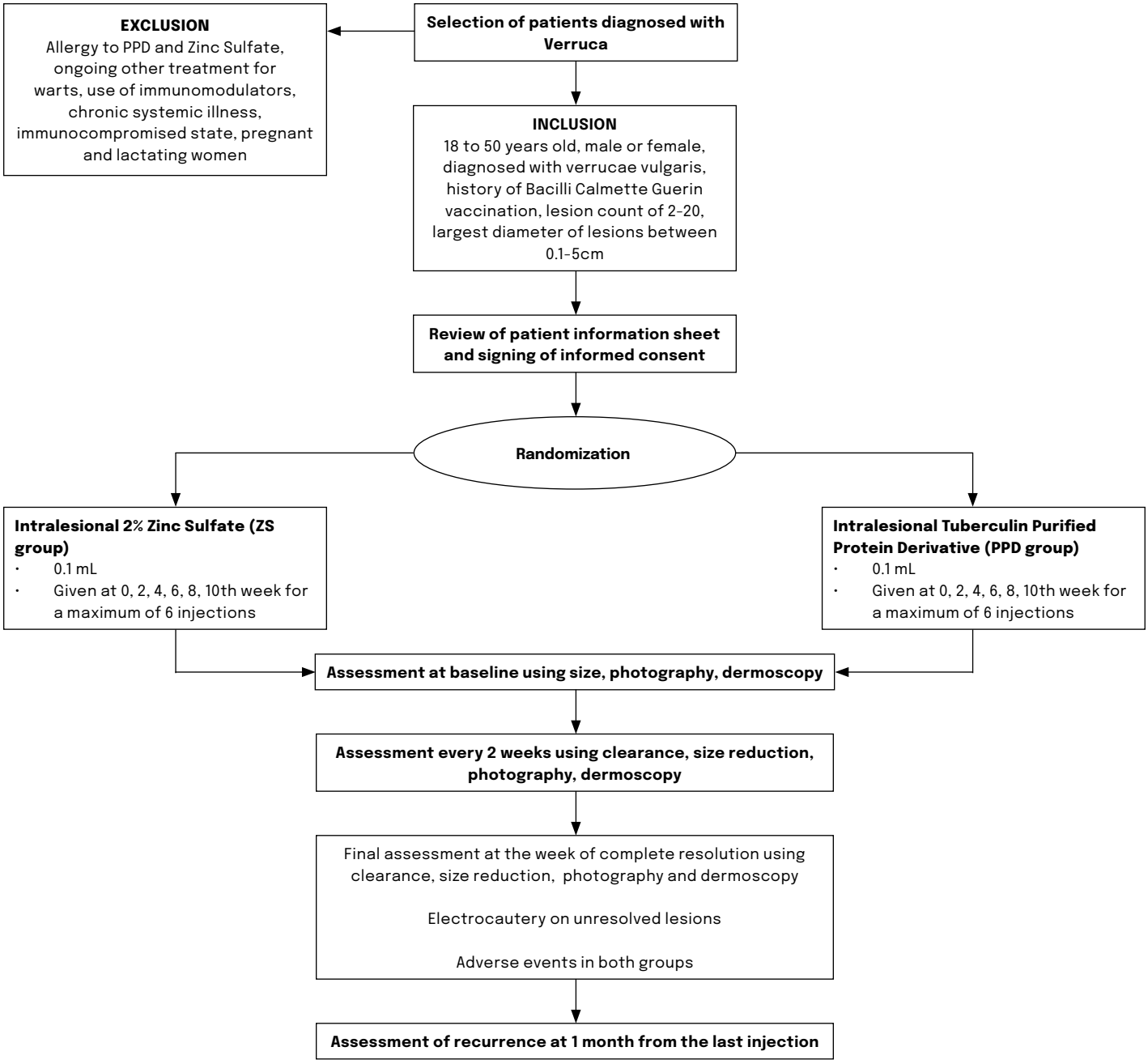

Figure 1. Schematic diagram of patient disposition for Zinc sulfate (ZS) and PPD groups.

repeated treatments of more than 6 weeks in duration with blistering and discomfort in the patients.[4]

The antiproliferative treatment for verruca consists of topical 5-fluouracil, podophyllotoxin, bleomycin, cidofovir, and retinoids. All treatments are available in our setting; however, the prolonged duration and high cost of treatment are the deterrents in choosing these treatments. Occlusotherapy or the use of occlusion of duct tape on verruca had varying cure rates as well.[4]

Considering the limitation of these previously mentioned treatment modalities, immunotherapy may be a better treatment for verruca. Immunotherapy that induces a localized immune response against the virus, is now considered by many dermatologists because of ease of use, efficacy on distant lesions, less discomfort, and absence of delayed healing time. Intralesional immunotherapy utilizes the ability of the immune system to mount a delayed hypersensitivity response to the wart tissue and has been associated with the production of Th1 cytokines which activate the cytotoxic and natural killer cells to eradicate the HPV infection.[5] Therefore, intralesional immunotherapy may eradicate not only the target wart but also the distant warts by strengthening the immune system.

In a study done by Khozeimeh et al (2017), the patients who were given immunotherapy using intralesional candida antigen showed significant therapeutic response compared to cryotherapy.[6] Several studies reported on the efficacy of Tuberculin Purified Protein Derivative (PPD), Measles, Mumps, Rubella (MMR) vaccine, Trichophyton, Propionebacterium, Vitamin D, candida antigen, mycobacterium vaccine, Interferon-alpha, Interferon-beta, and Interferon-gamma. Other forms are via oral administration of zinc sulfate and cimetidine.[7] According to the network meta-analysis by Salman et al (2018), there are few controlled trials done using the treatment of intralesional candida antigen and propionebacterium.[7] Moreover, these treatment modalities are not readily available in our setting. In the same study, PPD and MMR were regarded as the top ranked treatment modalities in achieving complete recovery of initial and distant lesions in comparison to the other modalities.[7] The high cost of MMR in our setting, may be a limiting factor for our patients. However, tuberculin Purified Protein Derivative (PPD), used in tuberculin skin test, is widely available, cost effective and well-known in the Philippines. It is derived from the Mycobacterium Tuberculosis human strain.[8] Various studies were reported about its ability to treat warts.[7] The cost, availability and efficacy on viral warts of PPD served as the reason for choosing this as the control in this study.

Zinc sulfate is an compound that is available, affordable, and approved by the Food and Drug Administration in the Philippines.[9] It plays a vital role in regulating the inflammatory response. It could lead to the eradication of the HPV virus that causes viral warts.[10,11] Low zinc levels cause a decrease in natural killer (NK) cell activity, but supplementation with zinc can increase its cytotoxicity and killing activity.[11,12] This increase in NK cell activity can help in eradicating HPV, and consequently, clearance of warts. Immunotherapy using intralesional zinc sulfate was regarded as effective, but only few studies have been done.[13-15] Furthermore, these studies had lesser treatment sessions, did not expound on the effect of intralesional zinc sulfate on size of the lesion and had a short observation period. Considering the many health benefits from zinc,[16] its availability and the need of additional studies, a study on the efficacy and safety of intralesional zinc in the treatment of verruca was considered.

METHODS

A double-blind, randomized, controlled study was done in a tertiary hospital from January-June 2019. The study protocol was approved by the hospital's institutional review board and was conducted in accordance to the Declaration of Helsinki.

Inclusion criteria were 18 to 50 years old, male or female, with 2-20 warts with the largest diameter measuring 0.1-5cm, and a history of BCG vaccination. Exclusion criteria were those with the largest wart located on the tips of fingers and toes, genitals, eyelids, history of adverse reactions to zinc sulfate and tuberculin PPD, undergoing other wart treatment, immunocompromised state, history of tuberculosis or negative tuberculin test, active illness, pregnant or lactating women (Figure 1).

A primary investigator and two research assistants participated in the study. Prior to the start of the study, the first research assistant, who was not blinded to the study, assessed the eligibility of patients, assigned these patients with an alphanumeric identifier and generated the treatment allocation. The list of patient numbers were entered in www.randomization.com which randomly assigned the patients. The 2nd research assistant, who was blinded to the treatment allocation, assessed and recorded the treatment outcomes. The primary investigator, who was also blinded to the treatment allocation, administered the treatment to the patients and assessed the overall results.

Table 1. Outcome Assessment.[8]

Outcome	Definition
Cleared/resolved	Complete removal of the wart (injected largest target wart and non-injected distant wart)
Improved/evident clearance	Decrease in size by =/>50% of the original wart
Partial clearance	Decrease in size by < 50%
No change from the previous lesion	
Worsening	Increase in size of the wart from baseline

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PREPARATION AND INTERVENTION

The solution was prepared in the pharmacy of a tertiary hospital using 2g of zinc sulfate powder dissolved in 100ml of sterile distilled water, packaged in bottles and was subsequently autoclaved. The first batch of the solutions underwent sterility testing. A shelf-life of 1 month was observed.

The largest wart was injected intralesionally with an 0.1mL zinc sulfate or 0.1mL PPD (Arkray Healthcare Private Limited) every 2 weeks. After complete clearance of the wart or completion of 6 injections, the participants followed up after 2 weeks and 4

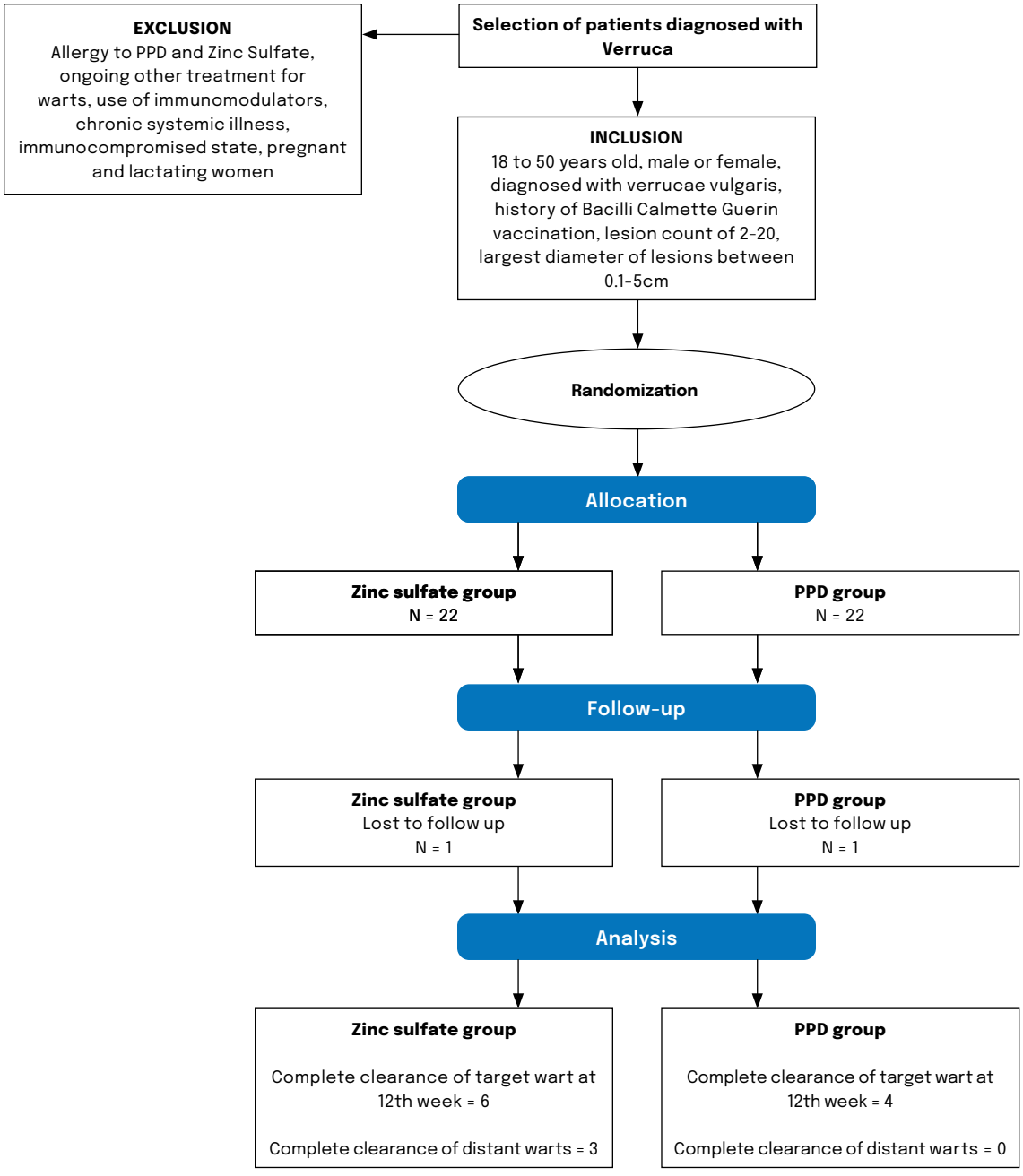

Figure 2. Consort flow diagram for Zinc sulfate and PPD groups.

weeks to assess for response and recurrence, respectively. In order to standardize the study, the same dose and schedule of treatment was used for both groups. The dose and schedule of treatment were based on a previous study[7] that used 0.1mL PPD every 2 weeks. Treatment was discontinued if withdrawal from study was requested, the patient was noncompliant, or there was intolerable adverse reaction that needed treatment.

CLINICAL ASSESSMENT

The primary outcome was the complete clearance of the injected largest wart. The secondary outcomes were reduction in size of the injected wart, percentage of patients with complete clearance of distant warts, recurrence after 1 month and adverse events.

At baseline and follow ups, photographs of all the warts were taken and measurement of the largest wart injected was done using a measuring tape (Table 1[8]). Clearance of injected target and non-injected distant warts was clinically indicated by complete resolution of the lesion with absence of black dots. Recurrence of warts was considered clinically when there was elevation of the lesion with presence of black dots. Using dermoscopy, dense papillae, whitish halos surrounding central red dotted vessels with hemorrhagic reddish to black dots or streaks were assessed at baseline.[18] Black dots signify thrombosed capillaries in warts which were examined during physical examination and dermoscopy. Disappearance of these findings confirmed complete resolution and absence of recurrence of the warts. Using a list of possible adverse reactions,[7] the 2nd research assistant examined each participant and asked about the effect of treatment which were recorded at each follow up. The possible adverse reactions were erythema, pain at injection site, pruritus, edema, hyperpigmentation, hematoma, scarring and vascular necrosis.[7] The participants were also asked if there were any side effects which were not found in the list. Pain medication and warm compress where used when necessary. Electrocautery was done on unresolved lesions during the last follow up.

SAMPLE SIZE DETERMINATION

PASS 2008 was used to calculate the minimum sample size of the study. The proportion of 87% complete clearance among patients given PPD was used.[12] A sample size of 38 patients achieved 82% power to detect at least a 40% difference in proportions given an alpha equal to 0.05. It was increased to 44—22 for each group—to account for 10% dropout. Convenience sampling design was employed.

DATA ANALYSIS

Data were encoded via Microsoft Excel. Stata MP version 14 was used for data processing and analysis. Continuous variables were presented as mean ± SD or median/IQR depending on data distribution while categorical variables were presented as frequency/percentage. Comparison of continuous variables were performed using independent t-test or Mann Whitney U test while comparison of categorical variables were done using Chi Square test or Fisher's exact test.

Chi square test or Fisher's exact test was utilized to compare the proportion of complete clearance and recurrence in the target wart between the two treatment groups. Percent clearance at each follow-up period was compared between the two groups using independent t-test. Reduction in target wart

Table 2. Demographic and clinical profile of patients with verruca vulgaris seen at a tertiary hospital (n=44).

Characteristics	Group ZS (n= 22) n(%)	Group PPD (n= 22) n(%)	P-value
Age (in years), median	27.50 [IQR: 20 – 46]	27.50 [IQR: 21 – 43]	0.7959[a]
Sex, n(%)			
Male	8 (36)	11 (50)	0.361[b]
Female	14 (64)	11 (50)	
Duration of verruca vulgaris, n(%)			
1-3 months	3 (14)	1 (5)	
3-6 months	3 (14)	4 (18)	0.767[c]
>6 months	16 (73)	17 (77)	
Total number of lesions, mean ± SD	5.18 ± 2.95	7.14 ± 4.62	0.1021[d]
Number of distant lesions, median (IQR)	3 [IQR: 2 -6]	6 [IQR: 2 – 8]	0.1272[a]
Size of largest lesion (in cm), mean ± SD	1.07 ± 0.44	1.03 ± 0.52	0.7792[d]
Location of target lesion, n(%)			
Palmoplantar	9 (41)	11 (50)	0.832
Periungual	8 (36)	6 (27)	
Upper extremity	2 (9)	3 (14)	
Lower extremity	3 (14)	2 (9)	

Table 3. Distant lesion location and size by group (n=229).

	Group ZS (n=137)	Group PPD (n=92)	P-value
Lesion site			
Face	1 (1)	0	0.376[a]
Scalp	4 (3)	0	
Upper extremities	16 (11)	7 (8)	
Lower extremities	4 (3)	1 (1)	
Palmoplantar	86 (63)	63 (68)	
Periungual	26 (19)	21 (23)	
Lesion size, median	0.30 [0.20 – 0.50]	0.40 [0.30 – 0.60]	0.0073[a,b]

[a]Fisher's exact test
[b]Mann Whitney U test

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Table 4. Median reduction in size (cm) of largest wart of patients compared to baseline seen in both treatment groups at a tertiary hospital (n= 44).

Follow-up	Group ZS (n= 22) Median [IQR]	Group PPD (n= 22) Median [IQR]	P-value[a]
2nd week	0.10 [0 – 0.20]	0.10 [0 – 0.02]	0.2913
4th week	0.30 [0.20 – 0.40]	0.20 [0.10 – 0.30]	0.2573
6th week	0.40 [0.30 – 0.60]	0.40 [0.20 – 0.50]	0.3872
8th week	0.50 [0.30 – 0.70]	0.40 [0.30 – 0.70]	0.3863
10th week	0.60 [0.40 – 0.80]	0.40 [0.40 – 0.90]	0.2895
12th week	0.70 [0.40 – 0.80]	0.40 [0.40 – 0.90]	0.2310

[a]Mann Whitney U test

Table 5. Proportion of patients showing complete clearance of distant lesions of patients in both treatment groups seen at a tertiary hospital (n= 44).

Follow-up	Group ZS (n= 22) n(%)	Group PPD (n= 22) n(%)	P-value
2nd week	0	0	-
4th week	0	0	-
6th week	0	0	-
8th week	0	0	-
10th week	0	0	-
12th week	1 (5)	0	1.000
14th week	3 (14)	0	0.232

size was analyzed using Repeated Measures ANOVA for within-group differences and One Way ANOVA for between group differences. Significant ANOVA results were further analyzed using Tukey HSD.

Intention-to-treat analysis was implemented wherein all patients with at least 1 follow-up were included in the analysis (i.e. available case). In order to determine if missing data on 2 patients can affect the study results, sensitivity analyses using simple imputation (last observation carried forward) and per-protocol analyses were performed on primary outcome (i.e. complete clearance of target wart). P values ≤0.05 were considered statistically significant.

RESULTS

A total of 44 patients participated in the study, randomly allocat-

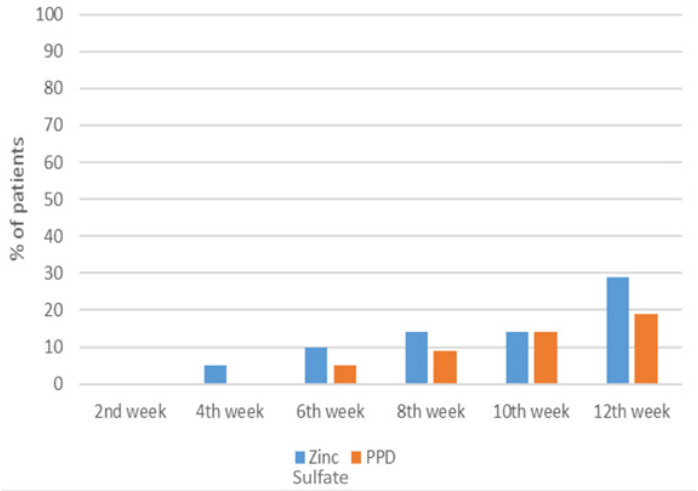

Figure 3. Proportion showing complete clearance of largest wart of patients in both treatment groups seen at a tertiary hospital (n= 44).[a]
[a]Fisher's exact test

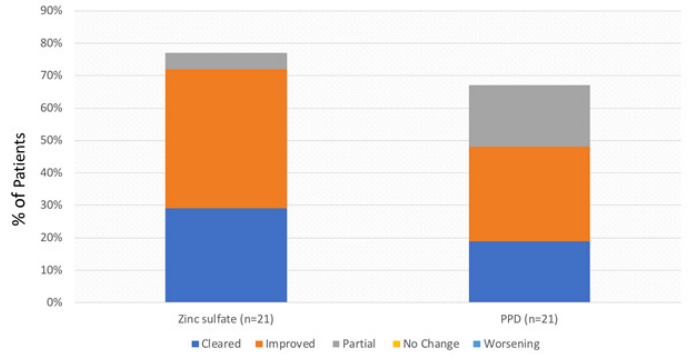

Figure 4. Treatment response at 12th week by group (n=42).

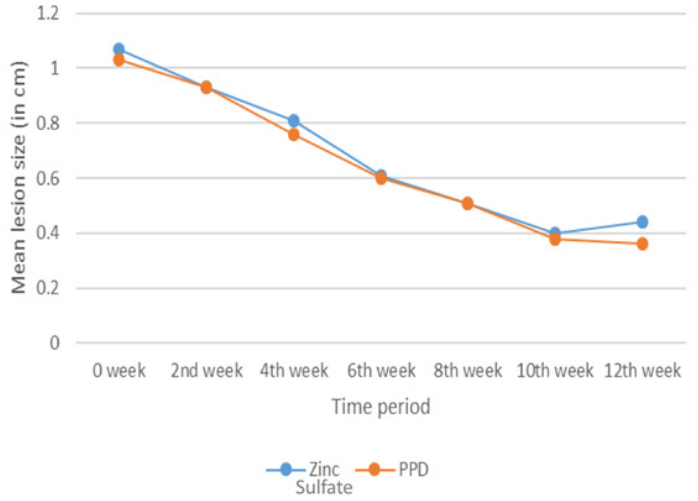

Figure 5. Mean size of target lesion over time by treatment group.

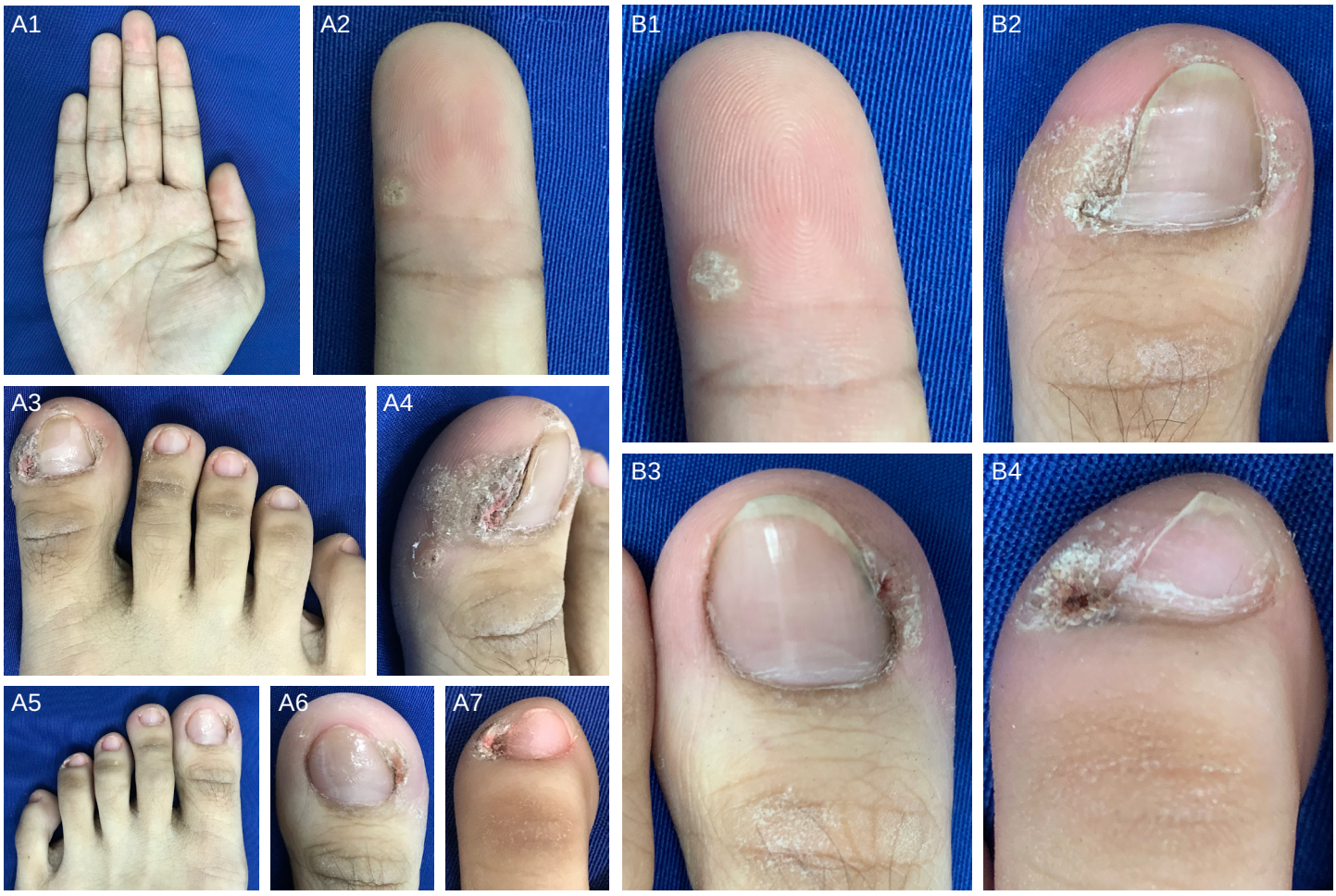

Figure 6. Patient with warts on the right index finger **(A1, A2)**, right big toe **(A3, A4)**, left big toe **(A5, A6)** and left 4th toe **(A7)** treated with PPD at baseline **(A1-A7)** and 12th week of follow up **(B1-B4)**.

ed to either Group ZS (n=22) or Group PPD (n=22). Two patients dropped out, one patient from Group ZS at the 4th week and one patient from Group PPD at 10th week (Figure 2). The follow-up rate was 95% for both groups.

A total of 44 patients, with 1 dropout from each group, were randomly allocated to either Group ZS or PPD (Table 2). The patients' age ranged from 18 to 53 years with a mean of 31.75 ± 11.83. A slightly higher proportion of patients were females (57%). The difference between the two treatment groups in terms of median age, sex, total number of lesions, median number of distant lesions, target lesion and location was not statistically significant.

Among the 44 patients included in the study, 279 distant lesions were recorded—137 in Group ZS and 92 in Group PPD. In both groups, most distant lesions were located in the palmoplantar area followed by periungual area. The difference of distant lesion site between the two groups was not statistically significant. However, the median size of distant lesions was significantly higher in Group PPD (Table 3).

The proportion of patients who achieved complete clearance of the target lesion at each follow-up period was compared (Figure 3). At 12th week, an increasing number of patients achieved target lesion clearance. A higher proportion of patients in Group ZS showed complete clearance compared to Group PPD except at 10th week. The differences in proportions did not reach statistical significance across all follow-up period.

At 12th week, a total of 10 patients – 6 (29%) in Group ZS and 4 (19%) in Group PPD – achieved complete resolution of target lesions (Figure 4). Improved to complete resolution of target lesion was higher in Zinc (71%) versus PPD (48%) group at 12th week, but the differences in proportion failed to show statistical significance (p=0.431).

Both groups showed a decline in mean lesion size over time (Figure 5) which was statistically significant (p<0.00001).

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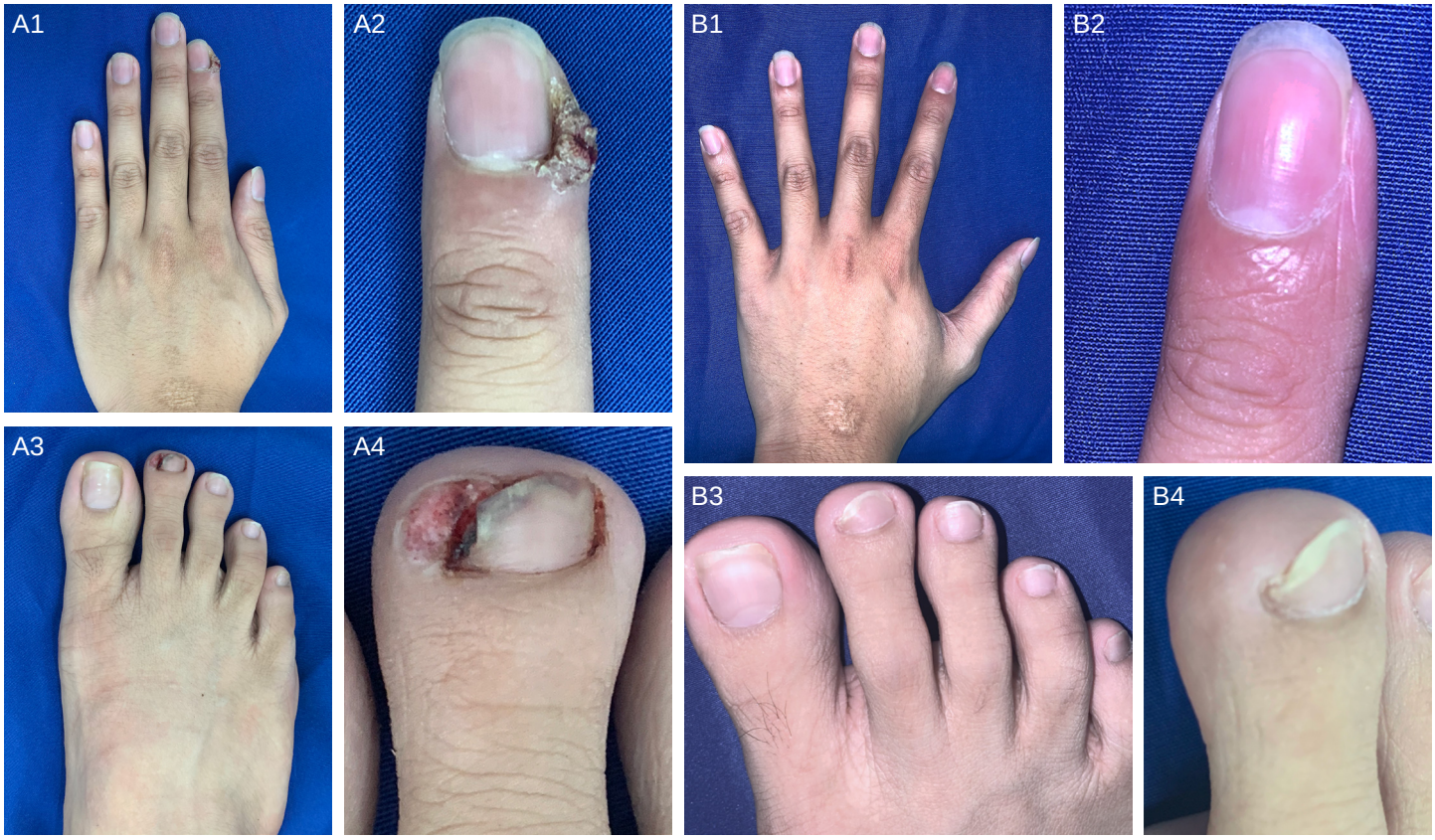

Figure 7. Patient with warts on the left index finger **(A1, A2)** and right 2nd toe **(A3, A4)** treated with zinc sulfate at baseline **(A1-A4)** and 12th week follow up **(B1-B4)**.

For Group ZS, the mean target lesion size at 6th, 8th, 10th and 12th week was significantly lower compared to baseline and 2nd week. For Group PPD, the mean target lesion size at 4th, 6th, 8th, 10th and 12th week was significantly lower compared to baseline (Figure 6).

The median reduction in size of the target lesion is higher in Group ZS compared to Group PPD except at 6th week (Table 4). However, the difference in median size reduction was not statistically significant.

Only three patients from Group ZS had complete clearance of distant lesions (Figure 7).

The difference in the proportion of patients who achieved total clearance at distant lesions between the two groups was not statistically significant (Table 5).

There were adverse reactions that developed in both groups (Table 6). A higher proportion of Group ZS developed erythema compared to Group PPD. The resolution of this adverse reaction was observed at 6th week. Pain at the injection site was higher in Group ZS compared to PPD. Pruritus was only experienced by 18% of Group ZS patients compared to 32% of Group PPD. Edema was observed in both groups but it continued in Group PPD until 10th week. Hyperpigmentation was observed in 1 ZS patient and 2 PPD patients. Only 1 patient in Group ZS developed hematoma at 2nd week. Scarring and vascular necrosis did not occur in both groups.

DISCUSSION

Zinc stimulates dendritic cells and activates both the innate and adaptive immunity to clear the virus.[12,11,16] Intralesional PPD administration increases IL-12 and activates T-cells to release gamma interferon which helps to eliminate the virus.[17,19-21] Repeated injections further boost the immune response.[8,19,22]

The current study revealed a lower percentage (29%) of complete wart clearance in Group ZS compared to other studies (60-98.2%)[13-15] where zinc sulfate was injected until blanching or bleb formation. In this study, a fixed dose was administered without blanching or bleb formation to standardize the dose similar to PPD and to avoid necrosis.[23] Studies have shown that complete clearance of injected warts was achieved by 60-94% with 0.1mL intralesional PPD[8,22,24-26] compared to 19%

Table 6. Adverse events in patients in both treatment groups seen at a tertiary hospital (n= 44).

Follow-up	Group ZS (n= 22) n(%)	Group PPD (n= 22) n(%)	P-value
Erythema, %yes	0	0	-
Percentage of patient with erythema			
2nd week	5 (23)	2 (9)	0.412
4th week	3 (14)	1 (4)	0.345
6th week	0	2 (9)	0.488
8th week	0	0	-
10th week	0	1 (5)	1.000
12th week	0	0	-
Pain at injection site, %yes			
2nd week	16 (73)	9 (41)	0.033*
4th week	7 (33)	4 (18)	0.255
6th week	2 (10)	1 (5)	0.607
8th week	2 (10)	2 (9)	1.000
10th week	0	1 (5)	1.000
12th week	0	0	-
Pruritus, %yes			
2nd week	4 (18)	7 (32)	0.296
4th week	0	4 (18)	0.108
6th week	0	1 (5)	1.000
8th week	0	0	-
10th week	0	1 (5)	1.000
12th week	0	0	-
Edema, %yes			
2nd week	6 (27)	2 (9)	0.240
4th week	1 (5)	2 (9)	1.000
6th week	1 (5)	2 (9)	1.000
8th week	0	2 (9)	0.488
10th week	0	1 (5)	1.000
12th week	0	0	-
Hyperpigmentation, %yes			
2nd week	0	0	-
4th week	1 (5)	2 (9)	1.000
6th week	0	1 (5)	1.000
8th week	0	0	-
10th week	0	1 (5)	1.000
12th week	0	2 (10)	0.488

in the current study. Milante et al. concluded that multiple intralesional injection of PPD was superior to single injection of multiple warts but more painful.[27] The higher dose of zinc sulfate[13-15] and PPD[27] used in the previous studies could have elicited a better response but with more side effects such as increased pain in the injection site.

Moubasher et al. reported that the proportion of patients who achieved total clearance of the target site did not significantly differ between ZS and PPD.[15] The current study showed comparable efficacy between groups in clearing target lesions even when intention-to-treat analysis was performed.

Immunotherapy has an advantage of clearing both target and distant warts.[26,27] Pande et al. suggested that distant wart clearance is a product of strengthening the immune system by stimulation of cytokines and gamma interferon.[17] Three patients from Group ZS achieved clearance of distant warts compared to none in Group PPD although the difference was not statistically significant. Previous studies showed that intralesional PPD led to higher clearance of distant warts which can be attributed to 6-10 treatment sessions[15,22,24,26] compared to only 6 in this study. Immunotherapy decreases the recurrence of warts.[4,12,14,15,17] None of the six patients with resolved target warts exhibited recurrence.

Injection site pain observed in both groups were similarly observed in previous studies.[13-15] Injection site pain associated with pruritus was observed in group PPD. Edema and erythema were common in previous studies[22] but occurred less in PPD group. Observed adverse effects such as injection site pain, pruritus, edema and erythema may have been caused by the inflammatory reaction triggered by the intralesional zinc sulfate[11,12,28] and PPD antigen.[21]

A limitation of the study is non-inclusion of pediatric patients and participants' assessment of the treatment. Future studies on the effect of combining oral and intralesional zinc sulfate are suggested.[29]

CONCLUSION

Intralesional 2% zinc sulfate is efficacious and safe in the treatment of verruca vulgaris with effects comparable to intralesional PPD. The percentage of patients with improved to complete resolution of target and distant warts was higher in the zinc sulfate group compared to PPD, however, the difference did not reach statistical significance. The adverse effects of erythema and pain at injection site were higher in the zinc sulfate group. However, pruritus was higher in the PPD group. Edema was observed in both groups but the duration was longer in the PPD group.

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