Comparative evaluation of oral valacyclovir versus oral zinc sulfate in the treatment of cutaneous verruca: a hospital-based, prospective clinical study

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Background: Cutaneous verrucae (warts) are benign epithelial proliferations caused by human papillomavirus (HPV). HPV acts by upregulating epithelial cell replication and downregulating host immune responses. Hence, treatment could be aimed at the virus (via antiviral drugs like valacyclovir) or the immune system (via immunomodulators like zinc sulfate). It is important to identify which pathogenesis should be preferably targeted for safe and effective therapy. We aimed to compare the efficacy and safety of oral valacyclovir versus oral zinc sulfate in the treatment of cutaneous verruca.

Methods: Fifty patients clinically diagnosed with warts were randomly divided into two groups: Group A (n = 25), treated with oral valacyclovir (1000 mg/day), and Group B (n = 25), treated with oral zinc sulfate (400 mg/day). All patients were evaluated using a Visual Analogue Scale (VAS) and the Physician's Global Assessment (PGA) and were followed up for 12 weeks. The results were analyzed using R software version 3.6.0.

Results: A significant decrease in the number of warts from baseline to the fifth follow-up visit was noted in Group A ($P < 0.05$) but not in Group B ($P > 0.05$). Both the groups showed a significant improvement visit-wise ($P < 0.05$) with respect to both VAS and PGA scores, but Group A (25.00 ± 28.58 and 1.60 ± 1.61; $P < 0.05$) showed marked improvement compared to Group B (60.40 ± 8.89 and 2.96 ± 0.35; $P < 0.05$).

Conclusion: Oral valacyclovir is more efficacious than oral zinc sulfate in the treatment of cutaneous verrucae. Both are equally safe.

Keywords: valacyclovir, warts, zinc sulfate, *Papillomaviridae*

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INTRODUCTION

Cutaneous verrucae (warts) are benign proliferations of the skin and mucosa caused by the human papillomavirus (HPV) [1,2]. They have a prevalence of 2–20% among primary school children and even higher in adults [3,4]. Usually, HPV enters the body through epithelial barrier disruptions and inserts its DNA into the host genome, triggering the abnormal replication of cells. It also increases blood flow to the area to facilitate this abnormally rapid growth [1,2,5]. Furthermore, it downregulates the keratinocyte innate immune sensors and suppresses the type I interferon response, which

is critical for controlling the viral infection [6]. The appearance of warts is determined by the type of HPV and the location of the infection. For instance, HPV type 1 is associated with plantar warts [2,7]. Most warts are asymptomatic, but some may cause cosmetic disfigurement, moderate to severe discomfort, or localized pain. For example, compression and friction in patients with plantar warts can lead to bleeding, impaired ambulation, and reduced foot comfort [1]. Warts are usually benign and self-limiting but may develop into verrucous carcinoma in certain cases of genital warts and in immunocompromised individuals [2,8].

Of the various management strategies available, a Cochrane Review failed to identify the most reliable one conclusively [2,9,10]. Destructive treatment, although popular, poses the risk of peripheral spread around the lesion margins of the traumatized wart, indicating either HPV seeding or a failure to treat marginal subclinically infected tissues (koebnerization/pseudo-koebnerization) [11]. Since warts result from upregulated virus action as well as downregulated immune response, antivirals and immunomodulators could be the drugs of choice [2,5,6]. However, it is vital to identify which pathogenesis should be preferably targeted for safe and effective therapy. Acyclovir is a commonly used antiviral drug. Its prodrug formulation, valacyclovir, has greater oral bioavailability and requires less frequent dosing [12]. Valacyclovir converts to acyclovir in vivo, which utilizes viral thymidine kinase to transform to its active form, thus specifically targeting viral DNA and preventing replication of the virus in the host [12]. Zinc preparations are commonly used immunomodulators. For instance, zinc sulfate enhances cellular and humoral immunity, aiding in HPV elimination and wart resolution [13].

The present study was designed to compare the efficacy and safety of oral valacyclovir versus oral zinc sulfate in the treatment of cutaneous verruca.

MATERIALS AND METHODS

Study design ad settings

After obtaining ethical clearance from the Institutional Review Board, this hospital-based, double-blind, prospective, randomized controlled trial was conducted at a tertiary care hospital in Karad, Maharashtra, India from 2017 to 2019 (two years). This study complied with the Declaration of Helsinki guidelines and adhered to the applicable CONSORT (2010) guideline (Figure 1). A sample size of 25 patients per group (total 50 patients) was required to detect a significant difference. The sample size was calculated using the formula below:

$$n = \frac{Z^2 p(1-p)}{d^2}$$

$$n = \frac{1.96 \times 1.96 \times 0.8(0.2)}{0.16 \times 0.16} = 24.01$$

Where n is the sample size required, p is the power of the study (= 80%), d is the precision error of estimation (= 0.16), and Z is the table value of alpha error from the standard normal distribution table (= 1.96).

Selection criteria

Fifty patients, irrespective of age and gender, reporting to the outpatient section of this hospital department, clinically diagnosed with cutaneous verruca, and able and willing to comply with the study procedure were recruited into the study after providing written informed consent. Consent was obtained from the legal guardians in the case of minors. Patients under 16 years of age whose parents were not willing to give consent, those not available for regular follow up, patients undergoing blood transfusion, those with known hypersensitivity or intolerance to the study drugs, and those with a history of any clinically significant systemic disorders or laboratory anomalies or systemic medications that could potentially interfere with the evaluation were excluded from the study.

Grouping and randomization

We used the randomization table system to equally and randomly divide the patients into two groups. Group A (n = 25) received oral valacyclovir (1000 mg/day), while Group B (n = 25) received oral zinc sulfate (400 mg/day), according to the need and tolerability of the patients.

Outcomes

All patients fulfilling the inclusion criteria were examined thoroughly using clinical and laboratory

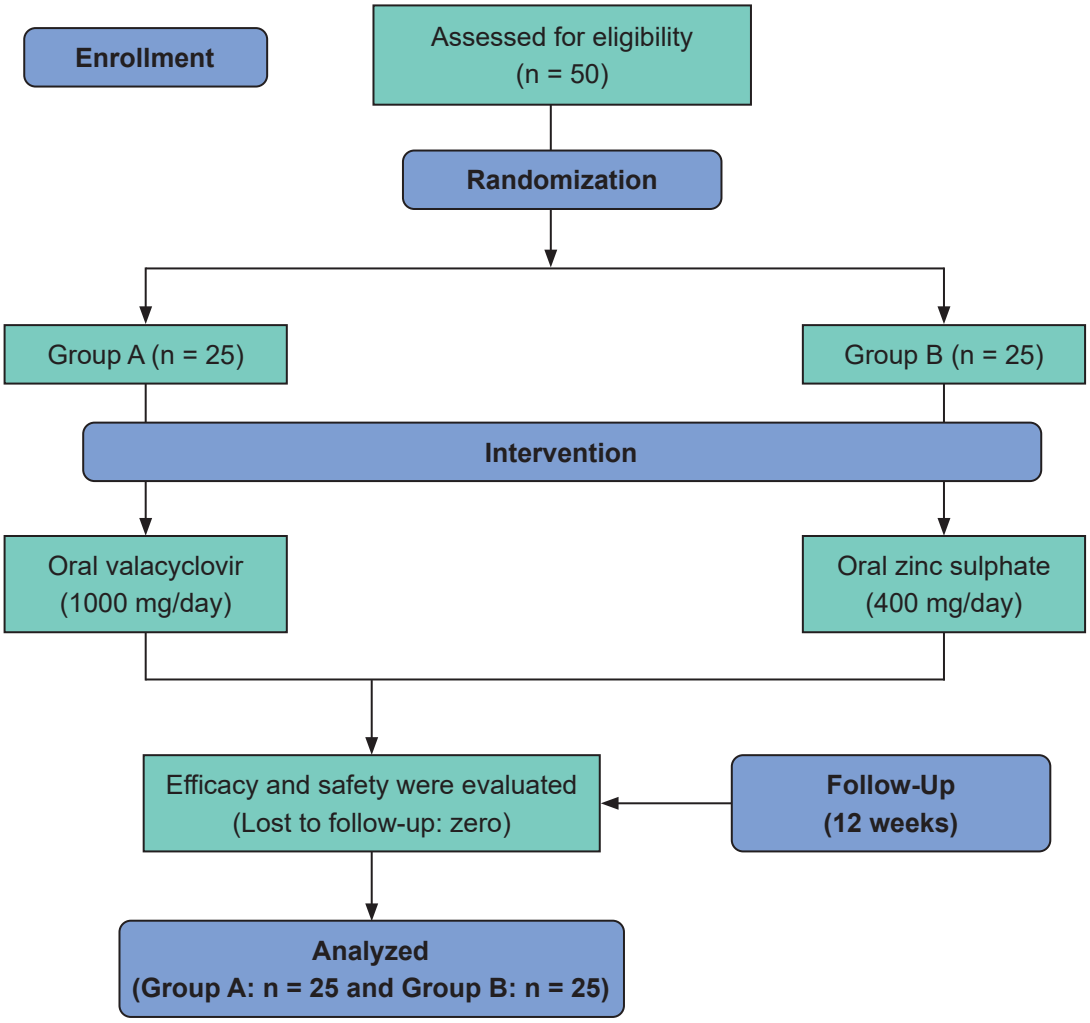

Figure 1. A CONSORT flow diagram of the study

measures for any underlying disease. All previous systemic or topical medications were stopped at least two months before the intervention and until the end of the study. Each patient was followed up regularly for 12 weeks to assess the safety and efficacy of the study medications. The follow-up visits were scheduled at the 2nd, 4th, 6th, 8th, and 12th weeks after baseline (day 0).

At baseline as well as at each follow-up visit, all patients were evaluated for the drug efficacy using a Visual Analogue Scale (VAS) [14] (for patient's perception of the outcome) and the Physician's Global Assessment (PGA) [15,16] (for disease severity), besides undergoing a physical examination. The patients were asked to mark the level of satisfaction on the 100-point VAS, with 0 indicating complete satisfaction and 100 meaning no satisfaction. The severity of the disease was assessed using the 7-point PGA, with 0 = clear, 1-5 = increasing severity, and 6 = worsened. Blood was withdrawn from all patients and sent to the laboratory for serological investigations (for serum urea and creatinine levels), performed at baseline, 2nd visit, and 4th visit. Clinical and investigational adverse events/findings were noted if present.

Statistical analysis

Data was collected, compiled, and analyzed using statistical software SPSS version 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Released 2011. Armonk, NY: IBM Corp.). Quantitative data were presented in the mean and standard deviation format. Comparison among the study groups was made with the help of the unpaired t-test as per the results of normality testing. Qualitative data

was presented with the use of frequency and percentage tables. Association among the study groups was assessed with the help of analysis of variance (ANOVA), paired t-test, and chi-squared test. P-values < 0.05 were considered statistically significant.

RESULTS

The study comprised 25 patients in each of the two groups, with a mean age of 24.40 ± 6.13 years in Group A and 24.96 ± 6.65 years in Group B. The most prevalent type of warts encountered were common warts (24% in Group A and 28% in Group B), followed by plantar warts (24% in Group A) and palmar warts (20% in Group B). Group A had an average of 4.88 ± 3.84 warts per person, while Group B had 4.48 ± 4.15 warts per person, with most patients having 0-4 warts (56% and 68% in Group A and Group B, respectively). According to the chi-squared test, no significant difference was found between the groups with respect to the distribution of age as well as the number and type of warts ($P > 0.05$). The frequency distribution of the study subjects based on age and clinical characteristics is shown in Table 1.

Table 2 presents the inter-group and intra-group comparison of the number of warts at different follow-up visits. ANOVA reveals a significant decrease in the number of warts from baseline to the 5th follow-up visit in Group A ($P < 0.05$) but not in Group B ($P > 0.05$). The student t-test indicated no significant difference between the groups in the reduction of the number of warts at any of the follow-up visits ($P > 0.05$). In both groups, no incidence of any adverse events or side

Table 1. Frequency distribution of study subjects based on age and clinical characteristics

Parameter	Subgroup	Group A (n=25)		Group B (n=25)		*P*-value
		No. of patients	Percentage	No. of patients	Percentage	
Age (years)	11-20	7	28%	6	24%	>0.05[C]
	21-30	14	56%	14	56%	
	31-40	4	16%	5	20%	
	Mean ± SD	24.40 ± 6.13 years		24.96 ± 6.65 years		
Type of wart	Common	6	24%	7	28%	>0.05[C]
	Plantar	6	24%	4	16%	
	Palmar	4	16%	5	20%	
	Flat	3	12%	3	12%	
	Genital	3	12%	3	12%	
	Periungual	2	8%	3	12%	
	Filiform	1	4%	0	0%	
Number of warts	0-4	14	56%	17	68%	>0.05[C]
	5-9	8	32%	5	20%	
	1-15	3	12%	3	12%	
	Mean ± SD	4.88 ± 3.84		4.48 ± 4.15		

[C] Chi-squared test of independence
Abbreviations: No, number.

Table 2. Inter-group and intra-group comparison of the number of warts at different follow-up visits

No. of warts	Group A			Group B			*P*-value
	Mean ± SD	Mean of diff	% diff	Mean ± SD	Mean of diff	% diff	
Baseline	4.88 ± 3.83			4.48 ± 4.15			>0.05[T]
Visit 1	4.76 ± 3.84	0.12	2.5%	4.48 ± 4.15	0	0	>0.05[T]
Visit 2	4.24 ± 3.77	0.68	13.9%	4.32 ± 3.87	0.16	3.5%	>0.05[T]
Visit 3	3.76 ± 3.41	1.12	22.9%	4.08 ± 3.80	0.40	8.9%	>0.05[T]
Visit 4	3.12 ± 3.31	1.76	36.1%	3.88 ± 3.64	0.60	13.4%	>0.05[T]
Visit 5	2.20 ± 3.29	2.68	254.9%	3.36 ± 3.07	1.12	32.8%	>0.05[T]
P-value	<0.05[A]*			>0.05A			

[A] Analysis of variance (ANOVA; intra-group comparison between baseline and last visit); [T] Student t-test (inter-group comparison);*Significant at 5% level of significance
Abbreviations: SD, standard deviation.

Table 3. Inter-group and intra-group comparison of clinical and investigative characteristics

Parameter	Timeline	Group A		Group B		*P*-value
		Mean ± SD	*P*-value	Mean ± SD	*P*-value	
Serum urea (mg%)	Baseline	32.00 ± 6.18	-	30.24 ± 5.95	-	>0.05[T]
	Visit 2	33.32 ± 7.53	>0.05[PT]	30.98 ± 6.23	>0.05[PT]	>0.05[T]
	Visit 4	33.84 ± 7.90	>0.05[PT]	31.08 ± 6.59	>0.05[PT]	>0.05[T]
	P-value	>0.05[A]		>0.05[A]		
Serum creatinine (mg%)	Baseline	0.94 ± 0.13	-	0.94 ± 0.15	-	>0.05[T]
	Visit 2	0.93 ± 0.16	>0.05[PT]	0.94 ± 0.15	-	>0.05[T]
	Visit 4	0.96 ± 0.21	>0.05[PT]	0.95 ± 0.15	>0.05[PT]	>0.05[T]
	P-value	>0.05[A]		>0.05[A]		
Visual Analog Scale (VAS) score	Baseline	100.00 ± 0.00	-	100.00 ± 0.00	-	>0.05[T]
	Visit 1	83.20 ± 9.45	<0.05[PT]*	99.20 ± 4.00	>0.05[PT]	<0.05[T]*
	Visit 2	65.20 ± 15.31	<0.05[PT]*	90.00 ± 10.80	<0.05[PT]*	<0.05[T]*
	Visit 3	49.60 ± 21.89	<0.05[PT]*	78.00 ± 7.07	<0.05[PT]*	<0.05[T]*
	Visit 4	35.20 ± 27.25	<0.05[PT]*	69.80 ± 8.72	<0.05[PT]*	<0.05[T]*
	Visit 5	25.00 ± 28.58	<0.05[PT]*	60.40 ± 8.89	<0.05[PT]*	<0.05[T]*
	P-value	<0.05[A]*		<0.05[A]*		
Physician's Global Assessment (PGA) score	Baseline	4.16 ± 0.90	-	4.04 ± 0.89	-	>0.05[T]
	Visit 1	4.00 ± 1.00	<0.05[PT]*	4.04 ± 0.89	-	>0.05[T]
	Visit 2	3.36 ± 1.32	<0.05[PT]*	4.04 ± 0.89	-	<0.05[T]*
	Visit 3	2.76 ± 1.30	<0.05[PT]*	3.56 ± 1.00	<0.05[PT]*	<0.05[T]*
	Visit 4	2.32 ± 1.52	<0.05[PT]*	3.24 ± 0.60	<0.05[PT]*	<0.05[T]*
	Visit 5	1.60 ± 1.61	<0.05[PT]*	2.96 ± 0.35	<0.05[PT]*	<0.05[T]*
	P-value	<0.05[A]*		<0.05[A]*		

[A]Analysis of variance (ANOVA; intra-group comparison between baseline and last visit); [PT]Paired t-test (intra-group comparison between specified follow-up visits); [T]Two independent sample t-tests (inter-group comparison); *Significant at 5% level of significance.
Abbreviations: SD, standard deviation.

effects was reported.

Table 3 summarizes the inter-group and intra-group comparisons of clinical and investigative characteristics. No significant difference was found between the groups in terms of serum urea and creatinine levels at any of the follow-up visits, according to the independent sample t-test ($P > 0.05$). ANOVA, too, revealed no significant changes in these levels within the groups at successive follow-up visits ($P > 0.05$). Inter-group comparison of the mean VAS and PGA scores (using the independent sample t-test) showed that these scores were significantly lower in Group A than Group B during all follow-up visits ($P < 0.05$), except for the PGA scores at the first follow-up visit ($P > 0.05$). These scores were comparable between the groups at baseline ($P > 0.05$). Within Group A, the paired t-test revealed a significant reduction in VAS and PGA scores across successive visits. Within Group B, the paired t-test showed a significant decrease in VAS scores at the 2nd, 3rd, 4th, and 5th visits ($P < 0.05$) and in PGA scores at the 3rd, 4th, and 5th visits ($P < 0.05$) only. Both groups showed a significant fall in both scores from baseline to the final visit, as per ANOVA ($P < 0.05$). This implies that both groups saw a reduction in disease symptoms (VAS score) and clinical disease severity (PGA score). However, the improvement was earlier and greater in Group A (valacyclovir treatment) than Group B (zinc sulfate treatment).

DISCUSSION

This study was conducted to compare the efficacy and safety of oral valacyclovir versus oral zinc sulfate in the treatment of cutaneous verruca. The underlying pathogenesis of warts is related to HPV-induced upregulation of cell replication and downregulation of immune responses [1,2,5,6]. Hence, an antiviral drug (valacyclovir) was compared with an immunomodulatory drug (zinc sulfate) in the present study. This is unique since no other study comparing these two oral medications could be found. The oral route of drug administration was employed to improve compliance. Valacyclovir, a prodrug, was used as it is an esterified version of acyclovir, with greater oral bioavailability (about 55%) than acyclovir (10–20%) [17].

The VAS was used for measuring disease-associated discomfort, while the PGA score was recruited for assessing disease severity. Both were significantly better in patients on valacyclovir than those on zinc sulfate. In a dose similar to the present study (1000 mg/day), oral valacyclovir was associated with the complete disappearance of plantar warts within 60 days in a study by Tandeter *et al.*, who also noted absolutely no drug side effects [18]. Bagwell *et al.* also described a case in which persistent plantar warts resolved after a ten-day treatment course of oral acyclovir [19]. Oral zinc sulfate was also associated with complete warts resolution within three months, without any side effects, by Gurkan *et al.*, similar to the present study [20]. In another study by Waqas *et al.*, the use of oral zinc sulfate (600 mg/day) for multiple recalcitrant viral verrucae resulted in complete eradication of warts in 62.2% of the patients and a 75% reduction in the number of warts, with 5% of the patients experiencing gastrointestinal side effects like nausea, vomiting, and abdominal pain [21]. Al-Gurari *et al.* also found oral zinc sulfate (600 mg/day) to be associated with 87% improvement of warts over three months, with 10% of patients experiencing nausea, vomiting, or diarrhea [13]. These findings are slightly different from the present study where 400 mg of the drug was used, yielding a 32.8% improvement rate without any side effects. The disparity in results could be due to larger doses of zinc sulfate used by Waqas N *et al.* and Al-Gurari *et al.*, or due to the longer drug course in the study of Al-Gurari *et al* [13,21].

In our study, the greater improvement in disease severity, discomfort, and the number of warts in the valacyclovir group compared to the zinc sulfate group could be because valacyclovir has a direct effect on the virus, while zinc sulfate affects the immune response to the virus [12,13]. Valacyclovir is converted by esterases to the active drug acyclovir and the amino acid valine via hepatic first-pass metabolism. Acyclovir is selectively transformed into a monophosphate form by viral thymidine kinase, which is subsequently phosphorylated to acyclo-GTP (a potent inhibitor of viral DNA polymerase) [12]. It has been reported that the viral enzymes cannot eliminate acyclo-GMP from the chain, resulting in the inhibition of further DNA polymerase activity. Acyclo-GTP is fairly rapidly metabolized within the cell, possibly by cellular phosphatases [12]. On the other hand, zinc sulfate acts by enhancing the immune response to the virus through modulation of macrophage and neutrophil functions, natural killer cell/phagocytic activity, and various inflammatory cytokines [13]. Hence, this study establishes the superiority of valacyclovir over zinc sulfate in the management of cutaneous verrucae. It could be interpreted that antiviral treatment is imperative to verruca management, while immunomodulatory treatment alone is not as effective.

However, this study has its limitations, including the use of a single-center approach with a limited sample size and short follow-up duration. Hence, multicentric, prospective studies with larger sample sizes and more extended follow-up periods are encouraged to validate the results.

CONCLUSION

Oral valacyclovir is more efficacious than oral zinc sulfate in the treatment of cutaneous verrucae. Both are equally safe. This study emphasizes the significance of antiviral treatment in managing cutaneous verruca since immunomodulatory therapy alone may not be as effective.

Conflict of interest: None declared.

REFERENCES

1. Al Aboud AM, Nigam PK. Wart. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431047/
2. Loo SK, Tang WY. Warts (non-genital). BMJ Clin Evid. 2009;2009:pii1710.
3. Kasim K, Amer S, Mosaad M, et al. Some epidemiologic aspects of common warts in rural primary school children. ISRN Epidemiology. 2013;2013:1-6.
4. Lutzner MA. The human papillomaviruses: a review. Arch Dermatol. 1983;119(8):631-5.
5. Massing AM, Epstein WL. Natural history of warts: a two-year study. Arch Dermatol. 1963;87(3):306-10.
6. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev. 2012;25 (2):215-22.
7. Jablonska S, Majewski S, Obalek S, et al. Cutaneous warts. Clin Dermatol. 1997;15(3):309-19.
8. Hazard K, Karlsson A, Andersson K, et al. Cutaneous human papillomaviruses persist on healthy skin. J Invest

Dermatol. 2007;127:116-9.

9. Scheinfeld N, Lehman DS. An evidence-based review of medical and surgical treatments of genital warts. Dermatol Online J. 2006;12(3):5.
10. Kwok CS, Gibbs S, Bennett C, et al. Topical treatments for cutaneous warts. Cochrane Database Syst Rev. 2012;9:CD001781.
11. Lipke MM. An armamentarium of wart treatments. Clin Med Res. 2006;4(4):273-93.
12. O'Brien JJ, Campoli-Richards DM. Acyclovir. An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs. 1989;37(3):233-309.
13. Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. Br J Dermatol. 2002;146(3):423-31.
14. Crichton N. Visual analogue scale (VAS). J Clin Nurs. 2001;10:697-706.
15. Freedman JD, Gottlieb AB, Lizzul PF. Physician performance measurement: tiered networks and dermatology (an opportunity and a challenge). J Am Acad Dermatol. 2011;64(6):1164-9.
16. Pascoe VL, Enamandram M, Corey KC, et al. Using the physician global assessment in a clinical setting to measure and track patient outcomes. JAMA Dermatol. 2015;151(4):375-81.
17. Soul-Lawton J, Seaber E, On N, et al. Absolute bioavailability and metabolic disposition of valacyclovir, the l-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother. 1995;39:2759–64.
18. Tandeter H, Tandeter ER. Treatment of plantar warts with oral valacyclovir. Am J Med. 2005;118(6):689-90.
19. Bagwell A, Loy A, McFarland MS, et al. Oral acyclovir in the treatment of verruca. J Drugs Dermatol. 2016;15(2):237-8.
20. Gurkan A, Özlü SG. Successful treatment with oral zinc sulphate of widespread plantar warts in a patient under systemic corticosteroid therapy. Eur J Ped Dermatol. 2015;25(4):215-7.
21. Waqas N, Khan SA, Naheed A, et al. Efficacy of oral zinc sulphate in the treatment of recalcitrant common warts. Journal of Rawalpindi Medical College. 2017;21(3):245-7.