Section: Dermatology

Original Research Article

EFFICACY OF TOPICAL SALICYLIC ACID WITH ORAL IMMUNOMODULATORS IN THE TREATMENT OF VERRUCA VULGARIS

Divyah P.[1], Umarani V.[2], P. Kannan[1]

[1]Assistant Professor, Department of Dermatology, Government Dindigul Medical College, Tamilnadu, India.
[2]Senior Resident, Department of Dermatology, Government Dindigul Medical College, Tamilnadu, India.

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Corresponding Author:
Dr. Divyah P.,
Email: divyah4dec@gmail.com

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ABSTRACT

Background: Verruca vulgaris is caused by human papilloma virus. The disease affects the extremities, knees, elbows, and trauma prone sites and is often asymptomatic. Warts treatment clearance depends upon the virus type, disease duration, and host immunity. Various treatment modalities for warts include topical, intralesional and systemic methods. The aim is to compare the efficacy of combination of topical salicylic acid with oral zinc sulphate, combination of topical salicylic acid with oral levamisole, combination of topical salicylic acid with oral ranitidine, and topical salicylic acid alone in the treatment of verruca vulgaris. **Materials and Methods:** Hundred patients were randomized to four groups, i.e., A, B, C, and D. 12% salicylic acid was combined with oral zinc sulphate in group A, with oral levamisole in group B, and with oral ranitidine in group C. Group D patients had 12% salicylic acid monotherapy. **Results:** The mean lesion numbers in group A declined from 7.16 at baseline to 2.84 at 8 weeks. The mean size of lesions in group A also reduced from 0.432 cm to 0.184 cm at 8 weeks ($p<0.001$). Moderate but significant improvement was also reported in group B. Group C and D had minimal changes that were not statistically significant. Group A also had the highest complete response (93.8%). No patient in group C and D had complete response. All patients have mild and non-significant adverse effects. **Conclusion:** Oral zinc sulphate with topical salicylic acid is a promising combination in the treatment of multiple verruca vulgaris.

INTRODUCTION

Human papilloma virus, an unenveloped DNA virus comprising about 8000 base pairs and about 55 nm in diameter causes verruca vulgaris (common warts). The virus infects the basal layer of the stratified squamous epithelium resulting in focal proliferation and expansion of the epithelial cells.[1] Verruca vulgaris are dome shaped hyperkeratotic papules or nodules. They have the size range of 1 mm to over 1 cm. They often affect the extremities, knees, elbows, and trauma prone sites. The disease is usually asymptomatic. However, it can cause tenderness when grow beneath the nail plate.[2] Warts are the common cutaneous viral infections and affect 7-12% of the population. The distribution and prevalence vary based on the population, age, and time periods. It affects about 10-20% of the school going children. Highest prevalence is reported in children and young adults.

Warts are directly transmitted through person to person contact and indirectly through fomites. Risk factors include using common swimming pools and bathrooms and autoinoculation.[3] HPV infection initiates a host-immune response resulting in infection clearance. Immune deficiencies affecting the T-cell response increase the risk of HPV infection, suggesting that that cell mediated immune response is essential for the control of HPV infection. Warts clearance depends upon the virus type, disease duration, and host immunity. Various treatment modalities, including topical, intralesional and systemic methods, are implemented successfully. Salicylic acid, a keratolytic agent, is used in the range of 10 to 60% for wart treatment. It causes destruction of the infected epidermal surface. Its liquid formulation can be applied daily, while the patches are reapplied every 48 hours.[4,5]

Deficiency of zinc reduces the immunity against cutaneous infections. Zinc homeostasis affects the functioning of the dendritic cells through toll like receptors. Zinc also possesses antiviral activity and inhibits the viral DNA crosslinking, thereby interfering viral replication. It also binds to the viral glycoproteins and prevents entry of the viral particles into the host cell.[6,7] Levamisole, an anthelminthic

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drug, acts as an immunomodulator in treating extensive warts. It alters the chemotaxis of polymorphonuclear leukocytes. It also has a role in scavenging free radicals.[8]

H2 receptor antagonists (cimetidine and ranitidine) are used for the treatment of warts. These drugs act as immunomodulators. H2 receptor downregulates the T-cell activation. H2 receptor antagonists works by blocking this receptor resulting in the T-cell activation.[9] The other treatment modalities for treatment of warts include hot water therapy, podophyllin, formaldehyde, retinoids, cryotherapy, radiofrequency ablation, laser, photodynamic therapy, and intralesional therapy. Although salicylic acid is considered a standard baseline therapy, head-to-head evaluation of various combinations of salicylic acid with salicylic acid monotherapy is lacking.[10]

Therefore, the study aimed to assess the efficacy of topical salicylic acid with oral zinc sulphate, topical salicylic acid with oral levamisole, topical salicylic acid with oral ranitidine and topical salicylic acid alone in the treatment of verruca vulgaris.

MATERIALS AND METHODS

This interventional study was conducted in the Department of Dermatology at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, between June 2017 and May 2018. Ethical clearance was obtained from the Thesis and Ethical Committee of Madras Medical College and Rajiv Gandhi Government General Hospital prior to commencement of the study.

Study Population: Patients attending the dermatology outpatient department with multiple verruca vulgaris during the study period were included in the study.

Sample Size: A total of 100 patients were included in the study, with 25 patients allocated to each treatment group.

Inclusion and Exclusion Criteria

Patients aged between 12 and 40 years with at least five common warts were included in the study. Pregnant women, lactating women, immunocompromised individuals, and patients receiving immunosuppressive medications were excluded.

Methods

All patients underwent detailed history taking and clinical examination, including assessment of wart type and lesion morphology. Patients were randomized into four groups (Groups A, B, C, and D) using block randomization method.

Group A received 12% topical salicylic acid ointment with oral zinc sulphate at a dose of 10 mg/kg/day in two divided doses. Group B received 12% topical salicylic acid ointment with oral levamisole at a dose of 2.5 mg/kg administered for two consecutive days per week. Group C received 12% topical salicylic acid ointment with oral ranitidine 300 mg twice daily, while Group D received 12% topical salicylic acid ointment alone.

The duration of treatment was 8 weeks, and patients were followed up at 2, 4, 6, and 8 weeks to assess treatment response. Response was graded as complete response when all lesions disappeared, partial response when there was at least 50% reduction in lesion number and size, and no response when there was no reduction in lesion number or size following treatment.

The primary outcome measure was treatment response at 8 weeks. Secondary outcome measures included reduction in lesion number and lesion size, time-based clinical response during follow-up, and adverse effects associated with treatment. Baseline demographic and clinical characteristics including age, gender, occupation, disease duration, family history, and previous treatment history were also recorded.

Statistical Analysis

Continuous variables were expressed as mean ± SD, while categorical variables were expressed as frequency and percentage. Comparison of continuous variables among the four groups was performed using one-way ANOVA followed by Bonferroni post hoc analysis. Categorical variables were analyzed using Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

The four groups were comparable at baseline with no statistically significant differences in demographic and clinical characteristics ($p>0.05$). The overall mean age of the study population was 23.14 ± 6.085 years, with the majority of patients belonging to the 21–30 years age group (51%). Mean disease duration ranged from 3.56 ± 1.044 months in Group D to 4.28 ± 1.208 months in Group A. Gender distribution, occupation, family history, and previous treatment history were also comparable among the groups. [Table 1]

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Category	Group A (S+Z)	Group B (S+L)	Group C (S+R)	Group D (SM)	p-value
Age (years)	Mean ± SD	25.56 ± 5.945	23.60 ± 6.494	21.44 ± 5.447	21.96 ± 5.898	0.07
Gender	Male	15 (60%)	15 (60%)	14 (56%)	12 (48%)	0.808
	Female	10 (40%)	10 (40%)	11 (44%)	13 (52%)	
Occupation	Labourer/Worker	12 (48%)	14 (56%)	16 (64%)	16 (64%)	0.614
	Student	13 (52%)	11 (44%)	9 (36%)	9 (36%)	
Disease Duration (months)	Mean ± SD	4.28 ± 1.208	4.00 ± 1.555	3.96 ± 1.136	3.56 ± 1.044	0.246
Family History	Present	1 (4%)	3 (3%)	4 (16%)	7 (28%)	NS

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	Absent	24 (96%)	22 (88%)	21 (84%)	18 (72%)	
Previous Treatment	Present	2 (8%)	3 (12%)	2 (8%)	1 (4%)	NS
	Absent	23 (92%)	22 (88%)	23 (92%)	24 (96%)	

Baseline lesion number and lesion size were comparable among all groups (p=0.066 and p=0.064, respectively). After 8 weeks, Group A showed the greatest reduction in lesion number from 7.16 ± 1.313 to 2.84 ± 2.095 (p<0.001) and lesion size from 0.432 ± 0.1406 cm to 0.184 ± 0.1344 cm (p<0.001). [Table 2]

Table 2: Comparison of Pre-treatment and Post-Treatment Number and Size of Lesions

Parameter	Timepoint	Group A (S+Z)	Group B (S+L)	Group C (S+R)	Group D (SM)	p-value
Number of Lesions	Pre-treatment	7.16 ± 1.313	7.12 ± 1.641	6.92 ± 1.320	6.28 ± 0.737	0.066
	Post-treatment	2.84 ± 2.095	6.00 ± 2.062	6.68 ± 1.282	5.88 ± 1.382	
Size of Lesions (cm)	Pre-treatment	0.432 ± 0.1406	0.380 ± 0.1041	0.348 ± 0.0770	0.384 ± 0.1068	0.064
	Post-treatment	0.184 ± 0.1344	0.252 ± 0.1085	0.292 ± 0.0812	0.312 ± 0.1691	

Progressive reduction in lesion number and size was observed over time, with better improvement was observed in Group A. Lesion count in Group A reduced from 7.16 ± 1.313 at baseline to 2.84 ± 2.095 at 8 weeks, while lesion size reduced from 0.432 ± 0.1406 cm to 0.184 ± 0.1344 cm. Clinical improvement appeared earlier in Group A at 4 weeks, whereas Group B showed delayed response at 6 weeks. Groups C and D showed minimal improvement throughout follow-up. [Table 3]

Table 3: Comparison of Lesion Number and Size at Various Time Periods

Parameter	Time point	Group A (S+Z)	Group B (S+L)	Group C (S+R)	Group D (SM)
Number of Lesions	Baseline	7.16 ± 1.313	7.12 ± 1.641	6.92 ± 1.320	6.28 ± 0.737
	2 weeks	7.12 ± 1.301	7.12 ± 1.641	6.92 ± 1.320	6.28 ± 0.737
	4 weeks	6.56 ± 1.261	7.00 ± 1.732	6.88 ± 1.333	6.28 ± 0.737
	6 weeks	4.88 ± 1.201	6.56 ± 1.938	6.80 ± 1.323	5.88 ± 1.236
	8 weeks	2.84 ± 2.095	6.00 ± 2.062	6.68 ± 1.282	5.88 ± 1.382
Size of Lesions (cm)	Baseline	0.432 ± 0.1406	0.380 ± 0.1041	0.348 ± 0.0770	0.384 ± 0.1068
	2 weeks	0.416 ± 0.1463	0.376 ± 0.1091	0.348 ± 0.0770	0.380 ± 0.1041
	4 weeks	0.324 ± 0.1268	0.340 ± 0.1080	0.344 ± 0.0768	0.368 ± 0.1282
	6 weeks	0.252 ± 0.1159	0.272 ± 0.1061	0.336 ± 0.0757	0.324 ± 0.1422
	8 weeks	0.184 ± 0.1344	0.252 ± 0.1085	0.292 ± 0.0812	0.312 ± 0.1691

Complete response was predominantly observed in Group A, where 15 patients (60%) achieved complete clearance, compared to only one patient (4%) in Group B and none in Groups C and D (p<0.05). Partial response was observed across all groups, while non-response was highest in Group C (48%). Adverse effects were minimal, with mild nausea and abdominal pain reported only in Groups A and B, whereas no adverse effects were observed in Groups C and D. [Table 4]

Table 4: Comparison of Treatment Response and Adverse Effects

Parameter	Category	Group A (S+Z)	Group B (S+L)	Group C (S+R)	Group D (SM)	p-value
Treatment Response	Complete	15 (60%)	1 (4%)	0	0	<0.05
	Partial	7 (28%)	15 (60%)	13 (52%)	16 (64%)	>0.05
	No Response	3 (12%)	9 (36%)	12 (48%)	9 (36%)	>0.05
Adverse Effects	Nausea	3 (12%)	4 (16%)	0	0	>0.05
	Abdominal Pain	4 (16%)	3 (12%)	0	0	>0.05
	Nil	18 (72%)	18 (72%)	25 (100%)	25 (100%)	>0.05

DISCUSSION

The study involved 100 patients with multiple verruca vulgaris randomized in four different groups (group A, salicylic acid with zinc; group B, salicylic acid with levamisole; group C, salicylic acid with ranitidine; group D, salicylic acid monotherapy). The study duration was 1 year.

Mean patient age in the study was 23.14 (± 6.085) years, with the age range between 12 and 37 years. Similar results were obtained by Waqas et al. (mean age: 22.02 ± 5.864 years; age range: 18-49 years).[10] Hassan et al. demonstrated higher prevalence of verruca vulgaris in children and young adults (38% in 11-20 age group and 51% in 21-30 age group).[11] Both sexes were affected, with slight male predominance. Forty-two percent were students while remaining were skilled or unskilled workers. Mean duration of the disease in the study was 3.95 months. Only 15% of the patients had positive family history. Majority (92%) of the patients had no history of treatment.

Group A had 25 patients of which 93.8% reported complete response, 13.7% had partial response, and 9.1% had no response. Group A showed the greatest reduction in lesion number and lesion size among all treatment groups. These results were similar to the

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result by Hassan et al. (60.9% complete response and 14.6% partial response).[11] Moniem et al. reported a complete response in 35% of the patients treated with zinc over a period of 1 month.[12] While Mun et al. showed complete resolution in 50% of the patients over a period of 2 months.[13]

In group A, abdominal pain and nausea were reported in 16% and 12%, respectively. The side effects reported in Stafeni et al. were nausea in 41.66% patients and vomiting in 16.66% patients.[14]

Hassan et al. has observed only mild abdominal pain in 6% of the patients treated with zinc.[11]

In group B, complete cure was reported in 6.2%, partial response in 29.4%, and no response in 27.3% patients over 2 months. Amer et al. has showed a complete resolution of warts to levamisole therapy in 60% of the patients over 5 months period.[15]

No patient reported complete response in group C. Karaman et al. showed complete response in 49% patients with ranitidine at as dose of 300 mg twice daily for 4 months,[16] while Orlow and Paller reported complete cure rate in in 81% of the patients with cimetidine with salicylic acid over a period of 2 months.[17]

None of the patients in group D had complete response, while 31.4% had partial response. Bruggink et al. reported complete response in 24% of the patients probably because of high salicylic acid concentration (40%).[18]

Dhar et al. showed complete response in 21% of the patients with wart paint containing 16.5% salicylic acid and 16.5% lactic acid over a 3 months period.[19]

Large-scale, multicentric randomized controlled trials should be done to compare the efficacy of different salicylic acid combination along with monotherapy. Dose optimization studies for zinc sulphate and levamisole should be conducted for treatment of warts. Some patients may require prolong treatment, thus safety profiling with extended duration therapy may be a topic for further research.

CONCLUSION

Topical salicylic acid combined with oral zinc sulphate demonstrated superior efficacy in the treatment of verruca vulgaris, with higher complete response rates and greater reduction in lesion number and size, along with minimal adverse effects.

Limitations

Being a single-center study, the findings may not be generalizable to the wider population. In addition, the relatively small sample size limits extrapolation of the study results. Larger multicentric studies with longer follow-up are required to validate these findings.

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