Original Research Paper

Volume - 12 | Issue - 11 | November - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Dermatology

COMPARISON OF EFFICACY OF ORAL LEVAMISOLE AND COMBINATION OF ORAL LEVAMISOLE WITH ZINC SULPHATE IN THE MANAGEMENT OF CUTANEOUS WARTS

Dr. Isha Singh	Assistant Professor, Department of Dermatology, Venereology & Leprosy, S.N. Medical College, Agra
Dr. Deepak Sharma	Assistant Professor, Department of Dermatology, Venereology & Leprosy, G.R. Medical College & J.A. Hospital, Gwalior
Dr (Lt.Col). K.S.Dhillon	Former Professor, Department of Dermatology, Venereology & Leprosy, Era's Lucknow Medical College & Hospital, Lucknow

ABSTRACT **Aim:** To compare the efficacy of oral levamisole and its combination with zinc sulphate in the management of cutaneous warts. **Method:** A total of 50 patients seeking treatment for cutaneous warts were randomized to two study groups of 25 patients each. Patients in Group A were given oral Levamisole (150 mg) on two consecutive days per week whereas patients in Group B were given oral Levamisole (150 mg) on two consecutive days per week along with oral zinc sulphate (10 mg/kg upto a maximum of 600 mg/day) upto a period of 3 months. Demographic and clinical profile, treatment history, local examination was performed. Type, site, nature and number of warts was noted. At final follow-up, clinical response was graded as: complete response (complete resolution), marked response (>70% reduction in size/number of warts), partial response (clearing or flattening of some lesions) and no response (no change or worsening) respectively. Student t-, Paired t- and chi-square tests were used to compare the data. **Results:** Mean age of patients was 18.42±6.88 years (range 9-32 years). Majority (66%) were males. Mean pre treatment number of warts was 8.16±4.89 and 8.48±3.25 respectively in Groups A and B. At three months mean number of warts was 3.56±4.33 and 0.84±2.44 respectively in the two groups. Complete to marked response was seen in 52% of Group A as compared to 84% of Group B patients ($p<0.001$). **Conclusion:** As compared to Oral Levamisole alone, its combination with Oral zinc sulphate was more effective in treatment of cutaneous warts.

KEYWORDS : Cutaneous warts, Oral levamisole, Zinc sulphate, Combination therapy, Complete response.

INTRODUCTION

Cutaneous warts (verrucae) are an extremely common, benign, and usually self-limiting skin disease. They are caused by infection of epidermal cells with the human papillomavirus (HPV). Although any area of skin may be infected yet hands and feet are the most commonly affected sites. Warts have a huge impact on the quality of life of patients. They tend to cause moderate to extreme discomfort in majority patients with impairment of social or leisure activities in nearly half the patients1. Treatment of warts is a difficult task as till date treatment of HPV infection remains elusive2. Hence the treatment strategies are primarily focused on the resolution of physical signs and symptoms only. Oral zinc sulphate is one of the most widely used and effective treatment of non-genital cutaneous warts3. The use of zinc sulphate is justified as patients with non-genital cutaneous warts are often known to have zinc deficiency. Levamisole, the levo-isomer of tetramisole, having been recognized as an anthelminthic agent is known to have a wide range of immunomodulatory actions. Its use in various dermatological disorders and skin infections/ infestations like warts, cutaneous leishmaniasis, HPV infection, superficial fungal infections, leprosy, pediculosis, pyoderma and HIV has been documented4. Both these drugs have been used effectively for treatment of warts, however, there is no study comparing the combined use of two drugs. Hence, the present study was planned to compare the efficacy of oral levamisole along against combination of oral levamisole with zinc sulphate for treatment of non-genital cutaneous warts using a randomized study design.

MATERIALAND METHOD

This randomized controlled study was carried out at Department of Dermatology, Era's Lucknow Medical College and Hospital, Lucknow over a period of one year after getting approval from the Institutional Ethics Committee

Sample size estimations were based on a study by Amer et al.5 with targeted response rate of 60% and 5% respectively in two groups. Sample size estimations were done at 95% confidence and 90% power. The calculated sample size was 13 for each group, however, after making contingency provisions, we proposed to carry out the study in a total of 50 patients, i.e., 25 patients in each group.

A total of patients seeking treatment for cutaneous warts were enrolled in the study after obtaining their informed consent. Patients having any pre-existing blood disorders, pregnant and lactating women, those having rheumatoid arthritis, severe renal impairment, having a history of immunomodulating drugs intake within 4 weeks prior to enrolment and those having a history of concurrent therapy with phenytoin were excluded from the study.

The patients were randomized into two groups using computer generated random number tables. Group A (n=25) received oral levamisole at a dose of 150 mg on two consecutive days per week orally and patients in group B were treated with oral levamisole 150 mg tablet on two consecutive days per week along with oral zinc sulphate (10 mg⁄kg to a maximum dose of 600 mg⁄ day) for a total duration of 3 months (or less if lesions resolve) and were reviewed at 2 weeks interval. The dose of levamisole was reduced to 100 mg for children between 8 to 12 years of age group.

At enrolment, demograhic information was obtained and a detailed general examination was carried out in all cases with particular reference to find out the distribution, type and size of the lesions.

Local examination was carried out methodically in every patient to find out the morphological features of every skin lesion. Routine haemogram, Renal Function Test and Liver Function Test was performed.

Response to therapy was evaluated and analyzed. Digital Photographs were taken, after taking informed written consent. The identity of the patient was kept confidential.

At the end of study, response to therapy was evaluated by taking into account the number and size of lesions and was graded using the following scale: (i) complete response; (ii) marked response (more than 70% reduction in size and/or number of lesions); (iii) partial response (clearing or flattening of some lesions);and (iv) no response or worsening of the disease.

Data Analysis: Data was analyzed using SPSS 18.0 software. Student t-, Paired t- and chi-square tests were used to compare the data.

RESULTS

Age of enrolled patients ranged from 9 to 32 years. Mean age of patients was 18.42±6.88 years. Majority of patients were males (66%), had ≤6 months since onset (66%), did not have any associated skin disease (88%) and had availed some treatment (68%) with homeopathic treatment being the most common mode of previous treatment (32%). Statistically, there was no significant difference between the two study groups with respect to age, sex, duration of onset, history of associated skin disease and its type and treatment

history (p>0.05) (Table 1).

Plane warts were most common type (50%) followed by common type (32%). Filiform (4%) and planter (14%) types were less common types. Face (54%) and upper limb (22%) were the most commonly affected sites. A total of 11 (22%) patients had koebnerisation. Number of warts ranged from 1 to 20. Mean number of warts in Groups A and B were 8.16±4.89 and 8.48±3.25 respectively. Statistically, there was no significant difference between the two groups with respect to clinical examination findings (p>0.05) (Table 2).

At final follow-up mean number of warts was 3.56±4.33 and 0.84±2.44 respectively in Groups A and B patients, thus showing the mean value to be significantly lower in Group B as compared to that in Group A (p=0.009). Patients in both the groups showed a significant reduction in number of warts at final follow up as compared to pre-treatment number (p<0.001) (Table 3).

At final assessment, proportion of those with complete response was 20% in Group A as compared to 76% in Group B. There were 8 (32%) patients in Group A and 2 (8%) in Group B showing marked response. Partial/no response was seen in 48% of Group A as compared to 16% of Group B patients. Statistically, there was a significant difference between the two groups with respect to treatment response (p<0.001) (Fig. 1).

DISCUSSION

The findings of the present study showed that combination of oral levamisole with oral zinc sulphate was highly effective in management of cutaneous warts as compared to oral levamisole alone. In the present study we did not notice any adverse effect of treatment in either of two groups and thus combination therapy was found to be safer and more effective as compared to oral levamisole solo therapy.

Although use of oral zinc sulphate alone or levamisole alone has also been documented to be successful in treatment of cutaneous warts previously too[4,5]. Use of combinations such as cimetidine with levamisole have been shown to be more effective than use of a single drug alone[6,7].

In their study, Parsad et al.[7] obtained cure rates of 45.5% in cimetidine treated patients and 85.7% in combination group (levamisole and cemitidine) treated patients and concluded that the combination of cimetidine with levamisole is more effective than cimetidine alone and is a highly effective therapy for the treatment. In the present study we also observed a similar trend endorsing the successful use of combination therapy as compared to monotherapy.

A higher success in combination therapy as observed in the present study could be attributed to the synergistic effect of the two drugs having two different mechanisms for warts resolution. Zinc being an essential trace element stimulates the functioning of many enzymes and transcription factors. It is crucial for all highly proliferating cells in the human body, especially the immune system, and innate and acquired immunity can be compromised by zinc deficiency[8]. Zinc has immunomodulatory effects that could counteract viral infections by having an effect on the synthesis of cytokines. In vitro, zinc induces the production of antiviral interferon (IFN)-a as well as IFN-c and it can potentiate the antiviral action of IFN-a[9]. In addition, clearance of viral infections requires cytotoxic T lymphocytes, which are highly dependent on zinc. In vivo, not only oral zinc sulphate but also topical zinc oxide has shown therapeutic efficacy in the treatment of viral warts[10]. Therefore, zinc can be a therapeutic option by modulating the immune system in a patient with viral warts.

On the other hand, Levamisole not only acts as an anti-inflammatory and anti-viral drug but also upregulates interleukin-2, interleukin-12 and interferon-γ by stimulating the T-helper-1 cells. Apart from this it also inhibits the action of endogenous immunosuppressive factors[4].

Cell-mediated immunity (CMI) is regarded as the principal mechanism for the rejection of warts, as histological changes in regressing warts are consistent with cell-mediated attack. High dose zinc and levamisole, both immunomodulator drugs, have been found to be effective in treatment of plane and common warts with varying success rates in earlier studies[3,4]. The findings of the present study show that combination of two makes them more effective.

The limitations of the study were follow-up duration, small sample size and inability to monitor the long-term impact in terms of recurrence after laying-off the treatment. Further studies on a larger sample size and longer duration of treatment with an eye on side effect profile and recurrence are recommended.

CONCLUSION

The findings of this study suggest that the combination of oral levamisole with zinc sulphate is worth considering as a therapeutic option for the treatment of viral warts. It is safe, cost- effective, efficacious and lacks serious side-effects.

Table 1: Basic characteristics of two groups

Basic characteristics	Group A (n=25) (%)	Group B (n=25) (%)	Total (n=50) (%)	t/χ2 value	p value
Age (yrs): Mean ± SD (Range)	18.36 ± 7.39 [9-32]	18.48 ± 6.48 [9-32]	18.42 ± 6.88 [9-32]	0.06	0.952
Sex:				0.09	0.765
Female	9 (36.0)	8 (32.0)	17 (34.0)		
Male	16 (64.0)	17 (68.0)	33 (66.0)		
Duration of Onset :				3.53	0.474
0-3 month	10 (40.0)	13 (52.0)	23 (46.0)		
4-6 month	5 (20.0)	5 (20.0)	10 (20.0)		
7-9 month	4 (16.0)	1 (4.0)	5 (10.0)		
10-12 month	4 (16.0)	2 (8.0)	6 (12.0)		
>12 month	2 (8.0)	4 (16.0)	6 (12.0)		
Associated skin disease:				0.76	0.384
No	23 (92.0)	21 (84.0)	44 (88.0)		
Yes	2 (8.0)	4 (16.0)	6 (12.0)		
Type of associated skin disease:				1.42	0.700
Atopic dermatitis	1 (4.0)	1 (4.0)	2 (4.0)		
Leprosy	0 (0.0)	1 (4.0)	1 (2.0)		
Molluscum contagiosum	1 (4.0)	2 (8.0)	3 (6.0)		
No	23 (92.0)	21 (84.0)	44 (88.0)		
Treatment taken in past:				2.23	0.694
Allopathic	3 (12.0)	5 (20.0)	8 (16.0)		
Ayurvedic	3 (12.0)	4 (16.0)	7 (14.0)		
Homeopathic	7 (28.0)	9 (36.0)	16 (32.0)		
Home remedy	2 (8.0)	1 (4.0)	3 (6.0)		
No	10 (40.0)	6 (24.0)	16 (32.0)		

Figures in parentheses are percentages

Table 2: Comparison of clinical examination findings between two study groups

Finding	Group A (n=25) (%)	Group B (n=25) (%)	Total (n=50) (%)	χ2 value	p value
Type of warts:				0.18	0.980
Common	8 (32.0)	8 (32.0)	16 (32.0)		
Filiform	1 (4.0)	1 (4.0)	2 (4.0)		
Plane	13 (52.0)	12 (48.0)	25 (50.0)		
Planter	3 (12.0)	4 (16.0)	7 (14.0)		
Site of warts:				0.47	0.925
Face	14 (56.0)	13 (52.0)	27 (54.0)		
Lower limb	3 (12.0)	2 (8.0)	5 (10.0)		
Soles	3 (12.0)	4 (16.0)	7 (14.0)		
Upper limb	5 (20.0)	6 (24.0)	11 (22.0)		
Koebnerisation:				0.12	0.733
No	19 (76.0)	20 (80.0)	39 (78.0)		
Yes	6 (24.0)	5 (20.0)	11 (22.0)		
Number of warts:				0.27	0.786
Mean ± SD (Range)	8.16 ± 4.89 (1 to 20)	8.48 ± 3.25 (5 to 16)	8.32 ± 4.11 (1 to 20)		

Table 3: Pre and post treatment change in number of warts in two groups

Groups	Pre treatment (n=25)	Post treatment (n=25)	Paired t value	p value
Group A	8.16 ± 4.89	3.56 ± 4.33	6.04	<0.001

Group B	8.48 ± 3.25	0.84 ± 2.44	12.09	<0.001
Student's t value p value	0.27 0.786	2.74 0.009	-	-

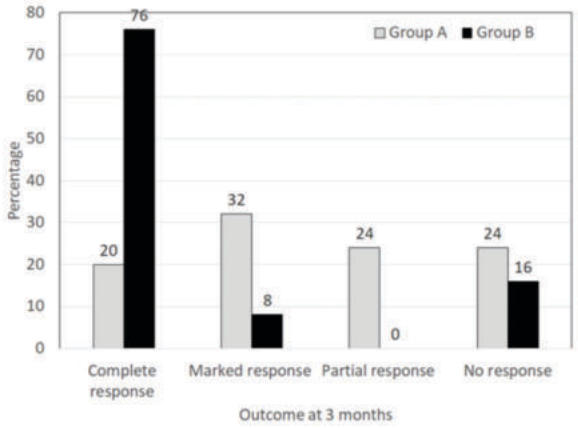

Fig. 1: Comparison of treatment response at 3 months (^{2}=18.17; p<0.001)

REFERENCES

1. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australias J Dermatol 2003;44:169–173.
2. van Brederode RL, Engel ED. Combined cryotherapy/70% salicylic acid treatment for plantar verrucae. J Foot Ankle Surg 2001;40:36–41.
3. Moniem EA, Genedy RM, Moussa R. Oral zinc sulfate in the treatment of recalcitrant warts. Egypt J Dermatol Venerol 2016;36:34-8.
4. Gupta M. Levamisole: A multi-faceted drug in dermatology. Indian J Dermatol Venereol Leprol 2016;82:230-6.
5. Amer M, Tosson Z, Soliman A, Selim AG, Salem A, al-Gendy AA. Verrucae treated by levamisole. Int J Dermatol 1991;30:738–740.
6. Parsad D, Saini R, Negi KS. Comparison of combination of cimetidine and levamisole with cimetidine alone in the treatment of recalcitrant warts. Australas J Dermatol. 1999 May;40(2):93-5.
7. Parsad D, Pandhi R, Juneja A, Negi KS. Cimetidine and levamisole versus cimetidine alone for recalcitrant warts in children. Pediatr Dermatol. 2001 Jul-Aug;18(4):349-52.
8. Prasad AS. Zinc in human health: effect of zinc on immune cells. Mol Med 2008; 14: 353–357.
9. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-alpha by leukocytes from elderly persons. J Interferon Cytokine Res 1997; 17: 469–472.
10. Khattar JA, Musharrafieh UM, Tamim H, Hamadeh GN. Topical zinc oxide vs. salicylic acid-lactic acid combination in the treatment of warts. Int J Dermatol 2007; 46: 427–430.