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# THE EFFICACY OF COMBINED USE OF ORAL LEVAMISOLE WITH ORAL ZINC SULPHATE IN THE MANAGEMENT OF NON-GENITAL CUTANEOUS WARTS: A PROSPECTIVE STUDY IN CHILDREN AND YOUNG ADULTS

Dermatology

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## ABSTRACT

**Aim:** To assess the efficacy of combined use of oral levamisole with oral zinc sulphate in the management of non-genital cutaneous warts in children and young adults. **Method:** A total of 25 patients aged <35 years seeking treatment 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: substantial response (>70% reduction in size/number of warts), fair response (50-70% reduction in size/number of warts) and poor response (<50% reduction in size/number of warts) respectively. Recurrence was assessed three months after completion of therapy. Data was analyzed using SPSS 18.0 software. Paired t- was used to compare the data. **Results:** Age of patients ranged from 9 to 32 years. Mean age of patients was 18.42±6.88 years (range 9-32 years). Majority (68%) were males had common/plane warts (80%) at face (52%) and without Keobnerization (80%). Mean number of warts was 8.48±3.25 before treatment and 0.84±2.44 after the treatment thus showing a significant reduction ($p<0.001$). Substantial improvement was seen in 84% cases, however, 4 (16%) were poor responders. Overall % reduction in mean number of warts was 90.1%. There were no adverse effects or recurrence. **Conclusion:** Combined use of oral levamisole with oral zinc sulphate was highly effective and safe in treatment of non-genital cutaneous warts in young children and adults.

## KEYWORDS

Non-genital cutaneous warts, Young children and adults, Oral levamisole and oral zinc sulphate combination therapy, Adverse effects

## INTRODUCTION

Non-genital cutaneous warts are amongst the leading causes for a dermatological consultation. They are primarily caused by viral infection caused by human papillomaviruses (HPVs) and can affect genitalia (genital warts) as well as non-genital/extragenital sites. Most of the times warts are benign in nature. Of more than 100 HPV strains identified to be associated with cutaneous warts, only 40 are associated with non-genital warts and malignancies. Warts are associated with both physical discomfort in terms of pain as well as in terms of psychosocial burden owing to their cosmetic significance. Treatment of warts often fails as it is associated with a high recurrence rate[3].

Although, viral eradication is the most effective treatment for cutaneous warts, however, it is not possible till now. Hence, the focus of alternative treatment strategies is on resolution of signs and symptoms using either destructive therapies like trichloroacetic acid, salicylic acid, podophyllotoxin, and 5-fluorouracil, radiocautery, cryotherapy, surgical excision, carbon dioxide laser[1,4]. There are non-destructive therapies like antimitotic, antiviral agents and immunotherapy. Different therapeutic modalities have their own characteristic efficacy as well as a side effect profile. The primary focus while planning a therapeutic intervention is on minimizing the side effects and recurrence.

Oral zinc sulphate is one of the most widely used and effective treatment of non-genital cutaneous warts[5]. 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 documented[6].

Both these drugs have been used effectively for treatment of warts, however, there is no study comparing the combined use of two drugs. We assume that hypothesize that combined use of both the drugs will be able to ensure an early resolution of warts and will have a positive impact on post-treatment immune status of the patients which will help to reduce the post-treatment recurrence too.

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.

## MATERIAL AND METHOD

This prospective study was carried out at Department of Dermatology of 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.[7] that reported a response rate of 60% for levamisole monotherapy. In the current study we expect a 50 to 55% increment in response rate with combined use of levamisole with oral zinc sulphate. Thus the targeted response rate was 92%. At 90% confidence and 10% precision, the calculated sample size was 22. After adding for a contingency we targeted a sample size of 25.

A total of 25 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.

All the received oral levamisole at a dose of 150 mg on two consecutive days per week orally 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 below 12 years of age. At enrolment, demogrrahic 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 thefollowing scale: (i) substantial response (more than 70% reduction in size and/or number of lesions); (ii) fair response (50-70% reduction in size and/or number of lesions);and (iv) poor response (<50% reduction in size and/or number of lesions).

All the patients were enquired telephonically regarding the warts status after three months. Patients reporting recurrence/worsening were invited for clinical evaluation.

**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 18.48±6.48 years. Majority of patients were males (68%), had ≤6 months since onset (72%), did not have any associated skin disease (84%) and had availed some treatment (76%) with homeopathic treatment being the most common mode of previous treatment (36%) (Table 1).

Plane warts were most common type (48%) followed by common type (32%). Filiform (4%) and planter (16%) types were less common types. Face (52%) and upper limb (24%) were the most commonly affected sites. A total of 5 (20%) patients had Koebnerisation. Number of warts ranged from 5 to 16. Mean number of warts was 8.48±3.25 (Table 2).

At final assessment, substantial, fair and poor response was seen in 21 (84%), 0 and 4 (16%) cases respectively ($p<0.001$). Mean number of warts after the treatment was 0.84±2.44 thereby showing a mean % reduction of 90.1%. Statistically, the improvement was significant ($p<0.001$). Post-treatment follow-up conducted three months after the completion of treatment did not show recurrence/worsening in any case (Table 3).

## DISCUSSION

The findings of the present study showed that combined use of oral levamisole with oral zinc sulphate was helpful to achieve very promising results, showing >90% reduction in number of warts and substantial clinical response in 84% of cases. This is very encouraging. In the previous studies use of oral zinc sulphate alone or levamisole alone has also been documented to be successful in treatment of cutaneous warts[6,7]. There is also evidence that levamisole when used in combination with other drugs has an increased effectiveness with cure rates as high as 85.7% in the combination group[8,9]. In the present study we also found similar outcomes when levamisole was used in combination with zinc sulphate.

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[10]. 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[11]. 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[12]. 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[6].

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[5,6]. The findings of the present study show that combination of two makes them more effective.

The present study also showed that the immune modulating actions of combined use of levamisole and zinc sulphate were sustainable even three months after the completion of therapy, thus showing its protective effect against recurrence. Considering the fact that recurrence is a major consideration while determining the treatment strategy for non-genital cutaneous warts, this combination seems to be a promising treatment option.

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

## CONCLUSIONS

Combined use of oral levamisole with oral zinc sulphate was highly effective in ensuring a high treatment success rate and protection against recurrence with safety, cost-efficacy and without any noticeable side effects.

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