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Manuscript Main Document "Topical Silver Nitrate in Combination with Oral Levamisole: An Alternative Modality in Recurrent Herpes Genitalis."

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Abstract
Context: *Herpes genitalis is a common sexually transmitted disease caused by herpes simplex virus for which no therapy is available which can cure its recurrence.*
Aims: *Comparative evaluation of therapeutic efficacy of topical silver nitrate ($AgNO_3$) in combination with oral levamisole in recurrent herpes genitalis.*
Methods and Material: *A total of 60 patients clinically diagnosed as recurrent herpes genitalis (with 2 or more episodes in last 6 months) with a positive Tzanck smear were divided into 2 groups (test and control) of 30 patients each. Patients in test group were treated with topical application of 10% $AgNO_3$, and then repeated every week, till lesions cleared, or for a maximum of 4 applications along with oral levamisole. In control group distilled water was applied. Patients were followed up for a total period of 24 weeks Results were analysed statistically.*
Results*: In test group only 12 (40%) out of 30 patients showed recurrence, whereas in control group 21 (70%) out of 30 patients showed recurrence.*
Conclusion: *Topical $AgNO_3$ along with oral levamisole has been found to be an effective therapeutic modality not only for treatment but also for preventing recurrence of herpes genitalis and prolonging remissions.*
Keywords: *Herpes genitalis, silver nitrate, levamisole*
Key message: *The most important problem about herpes genitalis is its recurrence, the only modality available being acyclovir suppressive therapy which is costly and has to be taken indefinitely. In our study topical $AgNO_3$ with oral levamisole was found as a cost effective and patient compliant alternative to suppressive therapy in recurrent herpes genitalis.*
Running title: *Topical silver nitrate with oral levamisole in recurrent herpes genitalis.*

I. Introduction

Herpes simplex virus (HSV) infection is caused by HSV 1 and 2, a DNA virus, with the predominant type being HSV2. One of the important characteristics of all herpes viruses is latency.[1] Herpes genitalis caused by HSV-2 is recurrent in 90% of cases. In herpes genitalis caused by HSV-1, 55% patient report recurrent episodes.[2] A number of drugs are used in the treatment of primary as well as recurrent herpes genitalis, but it should be noted that to date, there is no evidence, that any antiviral drug can affect the natural history of herpes genitalis in humans and curtail the recurrent nature of the disease.[1] So this study was being undertaken to evaluate the therapeutic efficacy of topical $AgNO_3$ in combination with oral levamisole in recurrent herpes genitalis.

II. Materials & Methods

A total of 60 patients clinically diagnosed as recurrent herpes genitalis (with 2 or more episodes in last 6 months) with a positive Tzanck smear (Fig1) were enrolled for study, after taking written informed consent, which were further divided in 2 groups of 30 patients each. Permission from ethical committee was obtained for carrying out this study.

Topical 10% silver nitrate was prepared by dissolving crystalline silver nitrate (99.8%) in distilled water and stored in amber colored bottles. Before application, the site involved was cleaned with distilled water, the vesicles if any were deroofed, and then 10% silver nitrate was applied at the erosion with a toothpick to avoid spill over. Immediately after topical application of 10% silver nitrate, erosions turned white, indicating the end point of application.

In test group, first application of topical 10% silver nitrate was carried out and then repeated every week, till lesions cleared, or for a maximum of 4 applications. Oral Levamisole (150mg was given, 1 tab EOD for 4 weeks, then 1 tab twice a week for another 8 weeks, for a total period of 12 weeks.
In the placebo group, only topical distilled water was applied weekly for 4 weeks.

First follow up visit was after 24 hours of first application to see any side effects e.g. erythema, edema, pain or appearance of new lesions. Next follow up visits were every week for first 4 weeks, then every two weeks for 8 weeks and then every four weeks for 12 weeks, completing a total period of 24 weeks, with a total of 12 follow up visits. At every follow up visit response to treatment was recorded and graded objectively.
G_0 = No improvement; G_1 = 25 – 50 % improvement; G_2= 51 – 75 % improvement; G_3 = 76 – 99 % improvement; G_4 = Complete recovery.
The results were analysed statistically.

III. Results

A total of 60 patients were enrolled for study, 30 in test group and 30 in control group. In test group 8 patients were of 15-29 year age group, 14 patients were of 30-50 years age group and 8 patients were more than 50 years of age. In control group, 12 patients were of 15-29 year age group, 10 patients were of 30-50 years age group and 8 patients were more than 50 years of age.

In the test group, 19 patients were heterosexual, 4 patients were bisexual, 3 patients were homosexual whereas 4 patients concealed their sexual history. On the other hand in control group 22 patients were heterosexual, 2 patients were bisexual, 3 patients were homosexual whereas 3 patients concealed their sexual history.

In the test group, 1 patient had associated molluscum contagiosum and 2 patients were VDRL reactive suggesting latent syphilis, whereas in control group 2 patients had associated balanoposthitis, and one patient had associated secondary syphilis and was VDRL reactive. In either group, no patient was HIV positive.

After the study it was found that in test group, only 11 patients had relapse, and 19 patients continued in remission whereas in control group 21 patients had relapse and only 9 patients stayed in remission.

All the patients showing recurrence during the follow up period were started suppressive therapy with oral acyclovir (1 tablet of 400 mg BD). Remission rate was higher in control group. No major side effects were seen in test group. Test group showed higher efficacy as compared to control group.

IV. Discussion

Although a number of drugs are available to treat the acute episodes of the disease, but no modality is available till date which can alter the natural course of the disease. Only acyclovir suppressive therapy is available which may help in prolonging the remissions, but again has to be taken indefinitely, thus adding to the psychological and financial burden of the patients.

Crystalline silver nitrate when dissolved in distilled water dissociates into silver ions and nitrate ions; nitrate ions combine with hydroxyl ions of water to form nitric acid which is a mild acid and may act as a mild chemical cauterizing agent which help in early healing of lesions. Shimuzu et al (1976) suggested that silver ions possibly cause the disruption of the viral envelope which may be responsible for its antiviral activity**.** In their study they showed that infectivity of herpes simplex virus type 1 and 2 were inactivated by silver nitrate at a concentration of 30µM or less**.**[3] There are no in vivo studies to evaluate the efficacy of topical silver nitrate in herpes genitalis till date to the best of our knowledge.

there are many studies which document the role of oral levamisole as a systemic immunomodulator in herpes simplex infections in vitro.[4,5] There have been clinical studies using oral levamisole alone or in combination with other agents, but oral levamisole with topical silver nitrate has never been used before, as per to the best of our knowledge. J Symoens and J Brugmans studied the therapeutic and prophylactic effect of Levamisole (150 mg) as the sole treatment for three consecutive days every fortnight. The results in herpes infections were promising.[96] We used levamisole in a different dosage, as described in methodolgy, but our study has also shown good results.

Patients with herpes progenitalis recurring every 14--28 days were treated with levamisole 150 mg orally twice weekly in an open trial carried out by O'Reilly RJ, Chibbaro A, Wilmot R, Lopez C, to evaluate the relationship between immunomodulation and clinical response. Eight of 12 patients studied for 4-9 months reported a decrease in the frequency of recurrences.[6] Again dosage of levamisole in this study is different, as compared to our study.

A double-blind study was carried out to investigate the possibility of therapeutic effect of levamisole on recurrent herpes progenitalis by Chang et al (1978). Levamisole, 50 mg three times daily for 3 days, was started at the first sign of recurrence. The study period consisted of 6 visits or 12 months, whichever came first. No statistical differences were observed between levamisole and placebo groups when comparing the duration of the lesion and the degree of pain, although less pain was observed among those on levamisole. The interval

between attacks was increasingly prolonged in the levamisole-treated group, and reached a significant level at the sixth visit.[7] We used a higher dose of levamisole for a shorter interval of time.

The effect of the immunomodulating drug levamisole was tested in 33 patients with frequently recurring attacks of herpes labialis or herpes genitalis by Jose et al (1980). Patients were randomly allocated to receive levamisole tablets, 2.5 mg/kg orally, on two consecutive days each week for 26 weeks, or placebo tablets taken for a similar time. Seven of 21 patients (33%) with recurrent herpes genitalis infection showed complete response and 10 (47%) showed a partial response while receiving levamisole. Three of 21 patients (14%) showed a partial response on placebo. Six of 12 patients (50%) with herpes labialis showed complete or partial responses, with three partial responses on placebo.[8] We used a different dosage, but for a similar duration of time and in combination with topical silver nitrate.

V. Conclusion

Topical Silver nitrate in combination with oral levamisole has been found to be an effective therapeutic modality not only for treatment but also for preventing recurrence of herpes genitalis and prolonging remissions. Out of 2 groups, a combination of topical silver nitrate with oral levamisole sulfate has been found to be effective both for treatment and preventing recurrence of herpes genitalis without many side effects. But still a large number of multicentric, randomized, controlled, trials are required to establish the role of topical silver nitrate and oral levamisole in herpes genitalis. We still recommend the use of topical silver nitrate in combination with oral levamisole as an alternative modality to acyclovir suppressive therapy, in contrast to which it is cost effective, simple, of limited duration and amenable to patient compliance, so as to reduce the financial, social and psychological burden of patients of recurrent herpes genitalis.

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Figure Legends

Fig 1. Tzanck smear examination showing acantholytic cells and giant cell

Figures And Tables

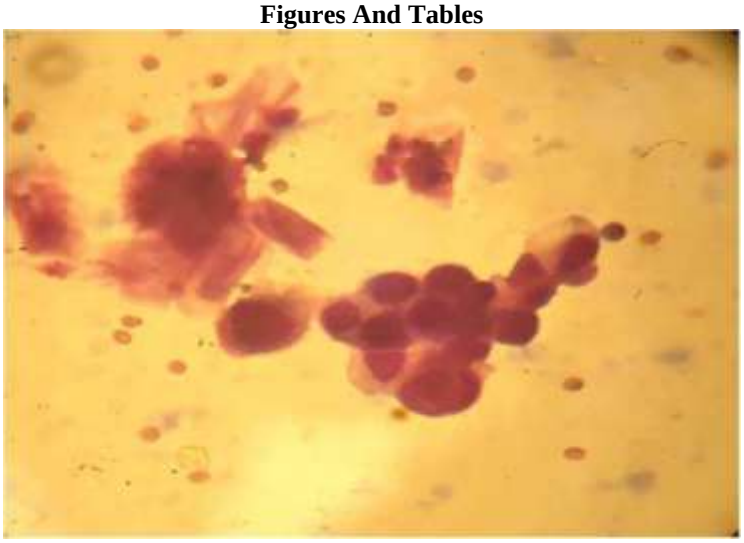

Fig 1. Tzanck smear showing acantholytic cells and multinucleate giant cell

Table 1–Distribution of patients according to their age

Age group (in years)	Test Group		Control group	
	No.	%age	No.	%age
15-29	8	26.66	12	40
30-50	14	46.66	10	33.33
>50	8	26.66	8	26.66
Total	30		30	

Table 2 – Distribution of patients according to their sexual behavior

Sexual Behavior	Test Group		Control group	
	No.	%age	No.	%age
Heterosexual	19	66.66	22	73.33
Bisexual	4	13.33	2	06.66
Homosexual	3	10	3	10
Concealed history	4	13.33	3	10
Total	30		30	

Table 3 – Distribution of patients according to presence of other sexually transmitted infections

Associated STIs	Test Group		Control group	
	No.	%age	No.	%age
Balanoposthitis	-	-	2	06.66
Genital warts	-	-	-	-
Syphilis	2	06.66	1	03.33
Molluscum contagiosum	1	03.33	-	-
Gonorrhoea	-	-	-	-
HIV +ve	-	-	-	-
Total	3	10	3	10

Table 4 – Distribution of patients according to presence or absence of recurrence (during follow up period)

Recurrence	Test Group		Control group	
	No.	%age	No.	%age
Present	11	36.66	21	70
Absent	19	63.33	9	30
Total	30		30	