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MANAGING RECURRENT GENITAL HERPES WITH ACYCLOVIR

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Seventy five patients of recurrent genital herpes (RGH) treated with oral or topical acyclovir and placebo were compared and followed for periods ranging 4 to 8 years in a prospective study. Oral acyclovir definitely helps RGH patients; it shortens healing time; postpones recurrences and instills confidence in the patients. There is sufficient evidence that RGH dies a natural death with time as seen after 8 years follow up in placebo group patients. Topical use of acyclovir cream is not as useful as believed.

Key Words : Genital herpes, HSV infections, Acyclovir

Introduction

Known since 1736,[1] genital herpes has emerged as a major public health problem. The causative organism, herpes simplex virus (HSV) has the ability to enter the latent state in the host and to intermittently undergo reactivation with lytic infection and virus replication. This capacity to cause recurrent infections is the major clinical problem of HSV infections. Genitally, the HSV manifests itself in two forms viz. first episode or primary (PGH) and recurrent genital herpes (RGH). Both serotypes 1 and 2 are known to affect the genital region. While the incidence of types 1 and 2 is approximately equal in patients with PGH,[2] type 2 is the predominant isolate in those with RGH.[3] The severity of clinical manifestation depends upon the previous exposure to the virus and the resultant sero-antibody-positivity. If prior HSV antibodies are present in individuals from previous exposures (likely event in the Indian patients), the primary episode of infection is going to be mild. At times, primary genital infections may be completely asymptomatic. Large percentage of RGH patients complain of prodromal symptoms of mild stinging or tingling at the genital site a few hours prior to the eruption. Occasionally, such symptoms are not followed by eruptions and it is regarded that the patient has had an abortive episode of RGH possibly because of a sufficiently good host immune response. It is worth noting that the HSV can survive on wet surfaces for several hours.[4] That may be the reason that the clinical manifestations of RGH tend to be more severe and longer lasting in women. The frequent recurrences of RGH for several years is the most bothersome aspect of the disease that interferes with the sexual relationship. Most patients get worried on account that it affects the genitals, its communicability to the partner and the fear that it will never be cured. In 1984, acyclovir was introduced for the treatment of HSV infections.[5] Subsequent reports [6,7] confirmed the beneficial effects of acyclovir in causing long term suppression of RGH.

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Patients and Methods

A prospective study was started in July 1984 to assess the effect of acyclovir treatment on patients with RGH. Clinical diagnosis was made from typical morphology and site of lesions displaying recurrent nature. When in doubt, cytological examination was made to confirm the diagnosis. Some patients who had earlier received acyclovir were excluded from this study.

Initially, it was decided to put all odd

number patients forming group A (Table I) on oral acyclovir 200 mg five times a day omitting the night dose for 5 days and all even number patients forming group B on topical acyclovir applications five times a day for periods until the lesions disappeared. In between some patients who either happened to be good acquaintance or with whom better rapport could be easily established and who could be easily approached were given placebo treatment forming group C in the form of multivitamin tablets for a period of two weeks each time they had recurrence.

Table I. RGH patients study groups

Group	Number of Patients	Age range	Sex	Marital status	Treatment given
A	30	20-30	28-M 2-F	20m 10um	Oral acyclovir 200mg 5 times a day for 5 days
B	15	21-30	15-M	10m 5um	Topical application of acyclovir cream 5 times a day for each recurrence until lesions remit
C	15	20-30	15-M	10m 5um	Placebo
D	15	21-36	15-M	10m 5um	Oral acyclovir 200mg 5 times a day for 5 days followed by 200mg 2 times a day for 6 months to 1 yrs

P<.001*

At the end of 6 years, 208 patients had entered the study; several of them did not complete the regular follow up and by July 1990, only 60 patients (Table I-30 patients in group A, 15 in group B and 15 in group C) were left with satisfactory regular follow up varying from 4 to 6 years in each group. Patients in group C have been followed up for 8 years now. From 1991 onwards it was decided that all new entrants be grouped in group D and put on oral acyclovir 200 mg 5 times a day for 5 days followed by 200 mg acyclovir orally 2 times a day for a further period of 6 months to a year. By the end of July 1994, 15 patients were on records who had been followed for a maximum period of 2 years having taken acyclovir for more than 6 months. Routine tests on blood and urine, blood urea, VDRL were obtained in all patients on oral acyclovir long term treatment. Liver function tests were done as and when required.

The age range, sex, marital status of patients and treatment given to them is shown in Table I. All patients in all 4 groups were advised to come for follow up on 3rd, 7th and 14th days and later as required; to keep in touch even if they were alright; to abstain from premarital or extramarital sex and from alcohol; to use condom if they wish to have sex during episodes and to avoid physical and mental stress as far as possible. During follow up, the actual healing time and any untoward effect of treatment were recorded in each patient.

Results

Of the total 75 patients who completed the study, 42 patients (56%) gave complaints suggestive of prodromal symptoms like tingling, burning, irritation at local site or along the penis or medial aspects of thighs and dysuria rarely, approximately one to 24 hours prior to the development of herpetic ulcers. Surprisingly, none of the patients remembered

having had attacks of PGH or HSV infections on other body sites prior to RGH lesions. Nor did they complain of any systemic symptoms that could indicate a primary episode of HSV infection in them. Nine patients complained of stinging in the urethra during episodes of RGH. There were 4 instances of conjugal infections in total and only two among the 75 patients presented here. During follow up, despite several married men having had occasional unprotected sex with their partners, not a single partner reported with infection.

The results depicted in Tables II,III and IV revealed-

recurrence-free (Table II).

3. It appeared that patients of RGH who sought treatment with oral acyclovir early became recurrence free earlier (Table III).

4. The mean annual number of recurrences per patient declined significantly from 6.7 to 2.8 in one year and then to 0.5 after 5 years of oral acyclovir regime ($p<.001$). With topical acyclovir treatment as well as with placebo there was a decline in mean annual number of recurrences per patient but only after 5 years.

5. Oral acyclovir therapy not only

Table II. Number of recurrence free patients each year

Group	Number of patients	Recurrence free patients per year 1st	2nd	3rd	4th	5th	6th	7th	8th	Average healing time before	after (days)
A	30	7	8	12	15*	16	14	-	-	7 - 10	4 - 5
B	15	0	0	1	1*	-	-	-	-	8 - 10	8 - 10
C	15	0	0	0	0*	2	5	7	8	6 - 8	6 - 7
D	15	1	2	4	5*	-	-	-	-	7 - 10	4 - 6

*$p<.001$

Table III. Group A RGH patients - Duration of disease vs acyclovir response

Duration (months)	Number of patients	Number of recurrence free patients per year 1st	2nd	3rd	4th	5th	6th
<6	17	7	8	9	10	12	10
7 - 12	3	0	0	2	1	1	2
13 - 24	6	0	0	1	1	1	2
25 +	4	0	0	0	1	-	-

1. There was a distinct shortening of average healing time of RGH lesions in patients on oral acyclovir treatment when compared to patients receiving topical acyclovir or placebo ($p<0.001$).

2. There was a significant rise in the number of recurrence-free patients per year in oral acyclovir group as compared to topical acyclovir and placebo groups ($p<0.001$). Placebo group C followed for upto 8 years revealed that more than 50% patients became

decreased the number of annual recurrences but also increased the time until the next post-treatment recurrence. Two patients in group D followed up during oral acyclovir treatment had shown recurrences while they were taking oral acyclovir.It did not appear that long term acyclovir regime in group D was any better than short term five day oral acyclovir treatment (Table IV).

6. Recurrences in all four groups were triggered by one or the other precipitating

Table IV. Mean annual number of recurrence per patients

Group	Number of patients	Mean annual number of recurrence per patient			
		prior to treatment	one year after treatment	2 years after treatment	5 years after treatment
A	30	6.7	2.8*	2.0*	0.5*
B	15	7.3	6.3	5.2	3.2
C	15	8.2	7.7	6.4	3.0*
D	15	6.4	2.8*	2.0*	-

P<.001*

factors which included physical fatigue, undue anxiety, febrile illness, alcohol intake, unprotected intercourse, masturbation and menstruation in one woman. Alcohol intake was the commonest precipitator. Several patients in group B experienced recurrences while they were still applying acyclovir cream. Two patients in group A had recurrences following large alcoholic drinks after years of recurrence free periods. Likewise, two patients in group D showed recurrences triggered by alcohol while they were still taking acyclovir orally.

7. Untoward side-effects of treatment were seen in some patients. These were gastrointestinal upset (4 patients), mild headache (3 patients), giddiness (2 patients), generalized weakness (2 patients) and marked drowsiness and sleep (1 patient) in patients in groups A and D receiving oral acyclovir. Three patients in group B receiving topical acyclovir complained of marked irritation at the site of application accompanied by slight exacerbation of the lesions.

Discussion

Oral acyclovir therapy definitely seems to help RGH patients; it shortens the healing time, postpones recurrences and instills confidence in the patients making it easier for them to recover. There is sufficient evidence that perhaps the disease dies a natural death with time. Oral acyclovir brings the patient to attain that goal sooner. Longer follow up of group D patients would suggest if long term use of acyclovir is better than short term use. In view of the expense involved in long term use and number of side effects seen in this study, a selective rather than routine approach should be better.

Topical use of acyclovir cream does not have any role in the treatment of RGH as seen in this study. It may perhaps be due to poor penetration of the drug to reach the virus. Newer second generation versions of acyclovir viz. valacyclovir and famcyclovir and a number of vaccine trials are on way. Until then oral acyclovir remains the only hope for patients with RGH.

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