Original Article

Acyclovir is not effective in pityriasis rosea: Results of a randomized, triple-blind, placebo-controlled trial

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ABSTRACT

Background: Acyclovir is considered to be an effective treatment for pityriasis rosea but randomized, blinded, placebo-controlled trials have not been performed. **Aims:** To test the efficacy of acyclovir in pityriasis rosea in a randomized, triple–blind, placebo-controlled trial. **Methods:** Twenty seven patients with pityriasis rosea were randomly allocated to receive placebo (n = 13) or acyclovir (800 mg five times daily for one week) (n = 14). The severity of disease was assessed by the pityriasis rosea area and severity index. Cure was defined as the absence of erythema, with no or minimal scaling. **Results:** The number of days (mean ± standard deviation) taken for cure was not significantly different between the two groups (placebo 26.54 ± 9.14 days versus acyclovir 33.29 ± 9.49 days; P = 0.0720, t-test; 95% confidence interval of difference –0.65 to 14.14 days). **Limitations:** The sample size for the present study was calculated using data from an earlier study. As the standard deviation was not mentioned in that article, a common standard deviation of fifteen days was assumed. A study with a larger sample size may be more effective in detecting minor treatment differences between acyclovir and placebo, if they exist at all. **Conclusion:** Acyclovir is not an effective treatment for pityriasis rosea.

Key words: Acyclovir, pityriasis rosea, randomized controlled trial

INTRODUCTION

Pityriasis rosea is a self-limiting disease, associated with the reactivation of human herpes virus-6 and/or human herpes virus-7.[1-3] Based on this association, it has been considered that acyclovir may be effective in treating the disease. In a non-randomized, single-blinded controlled trial where the control group received vitamin C tablets, acyclovir (in a dose of 800 mg five times daily for one week) was shown to be very effective in pityriasis rosea.[4] Subsequently, acyclovir (in a dose of 400 mg five times daily for one week) was also shown to be more effective than follow-up and studies comparing the efficacy of acyclovir and erythromycin have shown that acyclovir is more effective than erythromycin in pityriasis rosea.[5-7] A randomized controlled trial in which acyclovir was compared to vitamin C has also shown acyclovir to be effective.[8] The efficacy of acyclovir in pityriasis rosea been emphasized recently.[9]

We performed a randomized, triple-blind, placebo-controlled trial[10-12] to study the efficacy of acyclovir in pityriasis rosea.

METHODS

Setting, diagnosis and selection criteria

The study was performed in SS Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi between August 2012 and June 2013. Approval was

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obtained from the institutional ethics committee. Patients with pityriasis rosea were diagnosed on the basis of diagnostic criteria for the disease.[13] The inclusion criteria were (a) witnessed informed consent, given by the patient or parents in case of minors and (b) patients weighing 40 kg or more. Patients were excluded if any of the following was present: (a) pregnancy, (b) lactation, (c) expressed inability to come for weekly follow-up visits, (d) any treatment taken for the disease within the past one week, (e) any other illness as revealed by history and (f) history of a drug reaction to acyclovir. In all patients above eighteen, a VDRL test was performed in dilution. In addition, skin scraping and potassium hydroxide examination of each patient was done to rule out superficial fungal infections. If either of these results were positive, the patient was excluded.

Sample size

In a previous study, pityriasis rosea took an average of 18.5 days to clear in the treatment group, and 37.9 days in the placebo group.[4] We calculated the sample size for the present study using this data. As the standard deviation was not mentioned in that study,[4] a common standard deviation of 15 days was assumed for the purpose of sample size calculation. A sample size of 13 patients was calculated for each group, keeping an α (type 1 error rate) of 0.05 and β (type 2 error rate) of 0.1.

Severity assessment: Pityriasis rosea area and severity index

The pityriasis rosea area and severity index (PRASI) was devised for the purpose of the study. The severity of pityriasis rosea was assessed by grading erythema (E) and scaling (S) on a scale of 0 to 4. The area involved (A) was measured on a 0 to 6 scale on different regions of the body, namely the head (h), upper limbs (u), trunk (t) and lower limbs (l). The score ranged from a value of 0 to 48, and was calculated as follows.

PRASI = 0.1 (Eh + Sh) Ah + 0.2 (Eu + Su) Au + 0.3 (Et + St) At + 0.4 (El + Sl) Al

This was measured before initiating treatment and was measured again once every week until the patient was considered to be cured.

Randomization, treatment and blinding

Patients were randomly assigned to the two treatment groups using an online randomization tool (http://www.randomizer.org/). Twenty seven consecutive patients who fulfilled the inclusion criteria were included. They were randomly assigned to receive either 800 mg acyclovir or identical-looking placebo tablets, to be taken five times a day for one week. Both tablets were packaged in identical blister packs. They were given no other treatment and were examined once weekly until they were cured. Cure was defined to have occurred when there was complete absence of erythema (grade 0) and no or minimal scaling (grade 0 or 1). Patients were advised to take the tablets at specific times (6 am, 10 am, 2 pm, 6 pm and 10 pm) to minimize the chances of missing the doses.

The acyclovir tablets and identical-looking placebo tablets were provided by KLM Laboratories Pvt. Ltd., Mumbai. This company was requested to provide the study medications after the trial was planned by the authors, and it had no other role (e.g. initiating or conducting the trial, analysis of data, interpretation of results or deciding about its publication). The manuscript has not been shown to the company.

The code of treatment groups was broken after statistical analysis of the data. The investigators and statistician were unaware of the contents of treatments A and B until the data was completely analyzed.

Treatment allocation concealment

Treatment allocation concealment was done using the sealed envelope technique. Opaque envelopes were prepared for each patient by a person who was not involved in the study. These contained the randomization codes, treatment A or treatment B. After a particular patient was enrolled into the study, the envelope was opened to know which treatment was to be allocated.

Outcome measures

The main outcome measure was the number of days required for cure, after initiating treatment. The patient's assessment of response to treatment was also noted. The patients were asked whether they were unsatisfied, satisfied or very satisfied with the outcome.

In addition, an attempt was made to correlate patient age and disease duration, including the time required to achieve cure.

The data were analyzed using the Statistical Package for the Social Sciences version 16.0, and an online statistical tool (http://www.socscistatistics.com/). All P values are two-tailed.

Assessment of treatment adherence

Upon enrollment, the patients were provided treatment for one week in the form of pre-packaged blister packs. They were told to bring the used and partially used packs when they came for the second visit. This enabled us to assess the treatment adherence. On completion of the study, all the patients were again asked if they had any spare tablets left.

Trial registration

The trial was registered in the Clinical Trial Registry–India bearing the registration number CTRI/2012/09/002995.

RESULTS

Pretreatment characteristics of the patients

Of the thirty three patients who fulfilled the diagnostic criteria, twenty seven met the selection criteria. The two groups were comparable for all variables ($P > 0.05$), except for age ($P = 0.0088$). The patients in the placebo group were significantly younger, compared to those in the acyclovir group [Table 1]. None of the patients from either group had a positive potassium hydroxide examination or VDRL test or any systemic symptoms.

Follow-up visits

The patients were required to visit once weekly, but some came a few days late. Patient data were recorded on the dates of their actual visits. Patients were required to continue once weekly follow-up visits until cure was recorded. Thirteen patients in the placebo group completed 47 out of 48 follow-up visits. In the acyclovir group that comprised of fourteen patients, 63 out of 66 visits were completed. Two patients were each examined twice at their home itself; the above figures include these visits.

Table 1: Pre-treatment characteristics of the patients

Characteristics	Placebo group	Acyclovir group
Number of patients enrolled	13	14
Age (mean±SD)	18.31±2.66	24.43±7.31
Female (%)	3 (23.1)	5 (35.7)
Weight (mean±SD)	53.46±7.29	54.57±7.64
Duration of illness (median and interquartile range)	15.00 (6.50-19.00)	15.00 (7.00-20.00)
PRASI (median and interquartile range)	5.40 (3.30-7.55)	3.5 (3.2-4.9)
Number of patients with herald patch (%)	10 (76.92)	8 (57.14)

Number of days required for cure

The number of days (mean ± standard deviation) required for cure of pityriasis rosea was not significantly different between the two groups (placebo group: 26.54 ± 9.14 days vs. acyclovir group: 33.29 ± 9.49 days; $P = 0.0720$, *t*-test; 95% confidence interval of difference −0.65 to 14.14 days) [Figure 1].

The patient's assessment of response to treatment

When cure was recorded, the patients were asked whether they were unsatisfied, satisfied or very satisfied with the outcome. All patients reported that they were very satisfied.

Treatment adherence

Thirteen patients from the placebo group returned with 17 tablets at the first week of follow-up. In the acyclovir group, eleven patients returned with 19 tablets. Three patients in this group did not come with any tablet strips. This difference was not significant ($P = 0.3990$, Fisher's exact test). The patients who returned with a few tablets were asked to take them at four-hourly intervals. Upon completion of the study, patients were telephoned to ask for any remaining tablets. Only one patient in the placebo group had a tablet left.

Correlation between age of patients and the course of pityriasis rosea

Correlation was tested between the ages of the patients and the total course of the disease (duration of illness at presentation plus the number of days required for cure). The Pearson's correlation coefficient was −0.0821 and the coefficient of determination (R^2) was 0.0067.

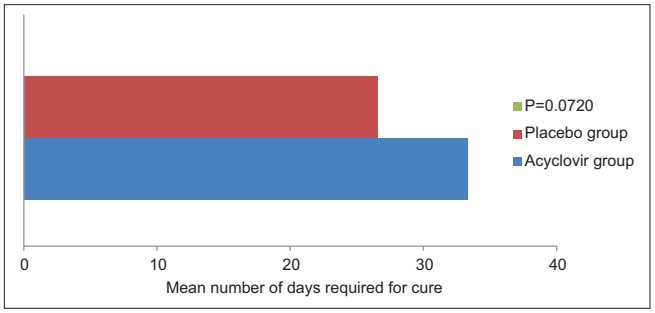

Figure 1: Number of days required for cure in the placebo group (mean ± standard deviation, 26.54 ± 9.14 days) and acyclovir group (33.29 ± 9.49 days); mean difference, 6.75 days; 95% confidence interval of difference, –0.65 to 14.14

Adverse effects

One patient in the placebo group complained of abdominal pain and diarrhea on the third day of treatment, which lasted for a day, and resolved without treatment.

DISCUSSION

Pityriasis rosea is a common, self-limiting, papulosquamous skin eruption that usually resolves over a period of 4–10 weeks.[14] Numerous studies have explored various pathogens such as bacteria, fungi and viruses as possible causes. Recent studies appear to provide evidence that reactivation of human herpes virus-7 and/or human herpes virus-6 is associated with pityriasis rosea.[1-3] Therefore, it is possible that acyclovir may be effective in the treatment of this condition. This has been tested in a few studies, which have suggested that acyclovir may indeed be effective.[4-8]

The results of our randomized, placebo-controlled, triple-blind trial with treatment allocation concealment show that acyclovir used in high doses (800 mg five times daily for one week) is not effective in pityriasis rosea. This is with regards to the number of days required for cure, which is the main outcome that matters to the patient in a self-limiting disease. We used a new scoring system for grading the severity of disease, the pityriasis rosea area and severity index (PRASI). This was inspired by the well-known scale for measuring the severity of psoriasis, the psoriasis area and severity index. There is no severity scoring system for pityriasis rosea in the current literature. As lesions of pityriasis rosea present with scaling and erythema, but not induration, we omitted the grading of induration from the psoriasis area and severity index and devised this pityriasis rosea area and severity index. Cure was defined to have occurred when there was complete absence of erythema (grade 0) and no or minimal (grade 0 or 1) scaling. This arbitrary definition was made, as it is difficult to determine whether minimal scaling is due to residual pityriaisis rosea, or due to other common condition such as xerosis. Positive patient satisfaction at the time of cure shows that our definition was valid.

It can be argued that the pityriasis rosea area and severity index has not been validated. However in our study, cure was defined to have occurred when there was complete absence of erythema (grade 0) and no or minimal scaling (grade 0 or 1). These endpoints are easily identifiable. Therefore, non-validation of the pityriasis rosea area and severity index will not affect the results of this study. The use of this index here may be seen in the light of absence of any established severity scoring system and as a pointer to the need of development of such a system.

When examining the pre-treatment characteristics of patients included in the study, it was observed that although both groups were similar with regards to most of the important variables, they were dissimilar with regards to the age. The patients who received placebo were significantly younger compared to those who received acyclovir. We wondered whether this affected our results and if there was any possibility of younger patients having a shorter course of disease. This was excluded when we found a very weak negative correlation between the ages of patients, and the total duration of their disease. This meant that younger patients in fact had slightly longer disease durations. Furthermore, there is no published data which suggests that the age of a patient influences the duration of pityriasis rosea. The present data may, in fact, be the first on whether the age of the patient influences the course of pityriasis rosea.

None of the patients in our study complained of any systemic symptoms. The absence of systemic symptoms suggests that viral reactivation may not have occurred in them. It may be that the reactivation of human herpes virus-7 and human herpes virus-6 plays an insignificant role in pityriasis rosea. This may be particularly true for the patients in the present study who had no systemic symptoms, with the result that acyclovir was found to be ineffective.

We calculated a pre-study sample size that provided an α (type 1 error rate) of 0.05 and β (type 2 error rate) of 0.1. It was calculated using the data from an earlier study.[4] As the standard deviation was not mentioned in it, a common standard deviation of fifteen days was assumed for the purpose of sample size calculation. We believe this to be reasonable. However, a different standard deviation will give rise to a different sample size. It is likely that randomized controlled trials with a larger sample size may detect treatment differences between acyclovir and placebo, if such differences exist at all. Based on our observations regarding the ineffectiveness of acyclovir, we understand that such small differences may not be clinically relevant.

The results of the present study are in contrast to earlier studies, which suggested that acyclovir is effective in pityriasis rosea. The previous studies included a non-randomized, single (patient)-blind, controlled trial (acyclovir in doses of 800 mg five times daily for one week versus vitamin C tablets),[4] treatment with acyclovir (400 mg five times daily for one week) versus follow-up[5] and studies comparing the efficacy of acyclovir and erythromycin.[6,7] A randomized, controlled trial in which acyclovir was compared to vitamin C showed acyclovir to be effective.[8] According to evidence-based medicine, the efficacy of a drug in self-limiting diseases can be determined by performing a randomized placebo-controlled trial.[10-12] The results of our study suggest that more research is needed to understand the pathogenesis of pityriasis rosea and to elucidate the role of human herpes virus-7 and human herpes virus-6 in this condition.

To conclude, our study shows that acyclovir is not an effective treatment of pityriasis rosea. However, we would hasten to add that this is not the final word on this issue. Replication of results by other studies is the cornerstone of science. When similar studies are followed by systematic reviews and meta-analyses, we will arrive at a clear understanding about the efficacy of acyclovir in pityriasis rosea.

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Conflicts of interest

There are no conflicts of interest.

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