Original Article

Treatment of Pityriasis Rosea With Erythromycin and Prednisolone: A Comparative Study

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Abstract

Background: Pityriasis rosea is a common dermatological eruption which is self-limiting with unknown etiology. Many therapeutic agents have been suggested for its treatment but none of them has gained a uniform consensus. Objective: To assess the efficacy of erythromycin and prednisolone in reducing the duration of PR. **Methods:** This is a systematic open placebo-controlled study and a comparative therapeutic trial conducted through the period from September 2008 to September 2009 in the Department of Dermatology and Venereology at the Al-Yarmouk Teaching Hospital. Total 75 patients were included in this study and their demographic information and history of disease, drug and family was recorded. Skin examination was conducted with focus on the distribution and morphology of the lesions. The patients presented within two weeks of the appearance of their rash were included and were divided into three groups (25 patients in each group). In group I, adult patients were given erythromycin capsules 250 mg for 4 times per day and children were given erythromycin syrup 25mg/kg in 4 doses/day. Adult patients in group II were given prednisolone tablets 20mg in two doses daily whereas its 0.5mg a day (2 doses) were given to children. Group III was a placebo group which received glucose capsules (100mg) four times daily. The duration of treatment was two weeks and every patient was seen at presentation and asked to attend for evaluation every two weeks until complete disappearance of rash. **Results:** In total, 75 patients completed this study of which 44 (58.67%) were females while 31 (41.33%) were males. The mean age of all patients was 19.19±13.75 years. After two weeks of treatment, the results showed that in erythromycin group, the symptoms got cleared in 76% of patients at the end of the two weeks as compared to prednisolone group (36%; P=0.005) and placebo group (12%; P=0.0000064). Prednisolone was found better than placebo with a significant statistical difference (p-value=0.05). The rash disappeared in 88% & 100% of erythromycin-treated patients, 60% & 84% of prednisolone-treated patients and 24% & 64% in placebo group patients at the end of four and six weeks of therapy respectively. Average number of days for PR to clear in erythromycin-treated patients was 16.32±8.74 days and in prednisolone-treated patients, it was 26.8±14.69. While in placebo group, it was 38.8±14.29 (P=0.001). Timing of initiation of treatment, whether it was started within the first week or the second week, showed minor impact on the course of PR in all therapeutic groups (P=0.26, 0.87 and 0.47 for erythromycin, prednisolone and placebo group respectively). **Conclusions:** Both erythromycin and prednisolone are found effective in reducing the duration of PR; however, erythromycin was found superior to prednisolone.

Keywords: pityriasis rosea, erythromycin, prednisolone

Introduction

The term pityriasis rosea (PR) means pink scales. It is a common, self-limited, acute dermatological eruption which typically starts as a single oval or rounded scaly plaque on the trunk. Also, smaller daughter lesions along the cleavage lines of the trunk appear in Christmas tree pattern.[1]

Access this article online

Quick Response Code:

Website: www.jnsbm.org

DOI: 10.4103/jnsbm.JNSBM_13_2_3

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Submitted: 01st August, 2022 **Received:** 06th August, 2022
Accepted: 23rd August, 2022 **Published:** 22nd September, 2022

How to cite this article: Salloom A S., Ahmed M J.E., Al-Sudany N K. Treatment of Pityriasis Rosea With Erythromycin and Prednisolone: A Comparative Study. J Nat Sc Biol Med 2022;13:102-109

Probably, Robert Willan was the first one who described PR in 1798.[2]

Epidemiology

Pityriasis rosea occurs in all races, and is relatively common throughout the world.[1] Its bimodal distribution is reported in Brazil and Singapore.[3,4] However, some studies show no variation in different seasons.[5,6] A study reported its incidence as 0.68 per 100 dermatological diseased patients.[7] A community-based study reported its incidence as 172.2 per 100.000 person per year.[8] The disease is more frequent in Africa i.e. about 2% of all patients examined, however, high variations have been seen ranging from 2.6% in South Africa to 0.5% in Kenya.[9] Although the female: male ratio is 1.5:1,[8] yet, some studies did not find statistically significant variation between both sexes.[10]

Mostly, the disease is prevalent in patients of age between 10-35 years, however, it may also occur in infants and in the ninth decade of life.[11]

Etiology

Although the etiology of disease is uncertain, yet so many clinical and epidemiological features may suggest an infective cause.[11] The powerful evidence against the infectious cause is absence of an infectious agent which might be involved in the etiopathogenesis of the disease.[12] Some studies also suggest that PR is a viral exanthem that is associated with reactivation of HHV-7 and/or HHV-6.[13-15] Eruptions like PR are also seen in many neoplasms[16-18] and bone-marrow transplantation.[19] Moreover, there are drugs which cause PR like eruptions.[11,16,20-29]

Pathogenesis

Examination under electron microscope shows that these virions are similar to HHV7. The presence of HHV7 close to the blood vessels in epidermis and dermis depicts that the virus may invades the extravascular dermal spaces and cause damage to dermal and epidermal tissues either directly or by interaction with the immune system.[30] Additionally, DNA of HHV6 and HHV7 is found in sera of PR patients. Also, their antigens are detected by using immunohistochemistry and in situ hybridization which confirms the replicative cycle of virus. All those findings suggest presence of viral infection at least in the acute stages of disease.[14,15] HHV7 acts as a primer that provides a transactivating action in the reactivation of latent HHV 6,[14,31] leading to the impaired detection of HHV7 in PCR test. This is the reason that HHV6 is detected in skin and many of the body tissues while HHV7 is not detected.[31]

Clinical Features

The PR eruption shows a constant course and pattern in about 80% of cases.[11] In classical presentation, patients experience a single truncal patch followed by multiple smaller lesions on the trunk after several days or weeks. The severity of itching is variable i.e. it is severe in 25% of patients, slight to moderate in 50% and absent in 25%. Minority of PR patients have flu-like illness which is associated with fever and malaise, headache, joint pain and decrease of appetite.[1] Around 69% of the patients show constitutional symptoms[32] while nearly 20% are presented with atypical symptoms.[1] These atypical clinical signs include primary plaque[1], generalized PR[11], unilateral PR[33], localized PR[34], pityriasis rosea inversa[35], vesicular PR[34], pustular PR[11], urticarial PR[34], purpuric PR[34], erythema multiforme[36], pityriasis rosea irritate [7] and pityriasis rosea gigantia of darier.[7]

Differential diagnosis of this disease include secondary syphilis[1], superficial tinea,[1,34] seborrheic dermatitis[11], erythema dyschromicum perstans (Ashy dermatosis) [34], guttate psoriasis[1] and pityriasis lichenoides.[1,11] Moreover, pityriasis alba[34], viral exanthem[37], tinea versicolor[37], gianoti crosti syndrome[34], erythema multiforme[34], urticaria[11], lichen Planus[11] and scabies Are also included.(38)

Treatment

Erythromycin[38,39] is a bacteriostatic macrolide which is used in treating the symptoms of PR. It interferes with protein synthesis of bacteria by binding reversibly with 50s unit of the ribosome.[40] It shows efficacy against intracellular pathogens by accumulating in macrophages and leukocytes. It also has immunomodulatory and anti-inflammatory efficacy which explains its effect in treatment of PR[7] Other than this, acyclovir[41-43] and phototherapy may also benefit patients with PR.[37,44]

Similarly, glucocorticoid which is an oral steroid, is also used for treatment of PR.[34] However, some studies have reported PR to become worse or even erythrodermic with its use.[45] Glucocorticoid works by passive diffusion of drug through the cell followed by binding to soluble protein receptor in the cytoplasm.[46] Also, steroid reduces the synthesis of many pro-inflammatory compounds such as ILs, cytokines, proteases and adhesion molecules. [47] It also effects the division and migration of many cells like eosinophils, lymphocytes and monocytes. [48] Likewise, cell apoptosis may also be triggered by glucocorticoid which can cause lymphocytopenia. [49]s Glucocorticoid therapy can not only cause leukocytosis due to demargination of WBCs from bone marrow[50] but also inhibition of neutrophil apoptosis.[51] In addition, this therapy also modulates inflammatory processes such as inhibitory effect on IL1, IL2, IL6 and TNF.[52,53] Additionally, phagocytosis and antigen processing cells (macrophages) are inhibited by glucocorticoid[54,55] which directly affects immediate and delayed hypersensitivity.

Side effects of systemic corticosteroid include pseudotumor cerebri and other psychiatric disorders, skeletal complications such as myopathy, aseptic bone necrosis, fracture and osteoporosis. Cataract with glaucoma is also

a complication of cortisol therapy. GIT complications like chronic pancreatitis and perforation and CVS complications like HT, retention of fluid and sodium andatherosclerosis can also occur. In addition, it can cause dermatological complications like urticaria, anaphylaxis, suppression of hypothalamic-pituitary-adrenal axis, growth failure and secondary amenorrhea.[56]

Study aim

To evaluate the effectiveness of erythromycin and prednisolone in reducing the duration of pityriasis rosea.

Methodology

It is a systematic open placebo-controlled and comparative therapeutic trial study. Total 98 patients were recruited in the study initially, however, 24 of them were dropped from the study due to unknown reasons and only 75 patients continued. The study was conducted in the Department of Dermatology, Venereology in Al Yarmouk Teaching Hospital through the period from September 2008 - September 2009.

A detailed history of patients was recorded and included their age, sex, occupation, residence (urban or rural), season of disease onset, duration at presentation, chief complaint and other associated symptoms. In addition, their drug history, previous treatments and personal and/or family history for such similar conditions was also obtained. Physical examination was done for every patient with focus on the type, distribution and number of lesions. Also all patients were sent to VDRL to exclude syphilis.

Patients were divided into 3 categories (25 individuals in each): group I patients were given 250mg of erythromycin ethyl succinate (erythromycin, SDI, Samarra, Iraq) capsules 4 times per daily for adults and 25mg/kg erythromycin ethyl succinate syrup (erythromycin, SDI, Samarra, Iraq) four times per day for children for 14 days. Group II patients were given prednisolone (prisolone, SDI, Samarra, Iraq) tablets (10mg) twice daily for adults and 0.5mg/kg twice/day for children for two weeks. Group III patients were given glucose capsules 100mg (as placebo) four times daily for two weeks.

Exclusion Criteria

The patients with the following conditions were excluded from this study:

1. Duration at presentation was more than two weeks.
2. Patients with diabetes mellitus or hypertension.
3. Patients with previous drug intake in the last two weeks prior to rash appearance especially corticosteroids, antihistamines and drugs which can cause PR-like eruption.
4. Pregnant women.
5. Immunocompromised patients.

Every patient was observed at presentation and was asked to attend for evaluation every two weeks until complete disappearance of the rash. Patients were clearly acquainted about the disease and its therapy and their consent was gained. Also, ethical approval of this study was obtained from the Ethical Committee of the Scientific Council of Dermatology, Venereology. Iraqi Board for Medical Specialization.

Statistical Analysis: Statistical analyses were done through descriptive and analytic statistics by using Chi-square and ANOVA considering p-value ≤ 0.05 as significant.[57]

Results

Total 98 patients were recruited in the study, however, due to unknown reasons, 75 patients continued with it. Of these, 44 (58.67%) patients were females and 31 (41.33%) were males and female to male ratio was 1.42:1. The mean age of patients was 19.19±13.75 years. Patients in the second decade of their life were the most common age group involved as shown in Figure1 And their age and gender distribution in different therapeutic groups is presented in Table 1.

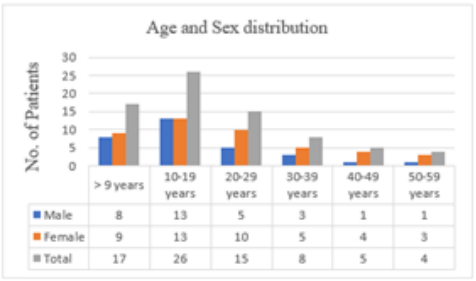

Figure (1): Age and sex distribution of patients with Pityriasis Rosea.

Table 1: Age and sex distribution of PR patients with each therapeutic category.

Parameter	Erythromycin	Prednisolone	Placebo
Age			
Range	4-50	3-51	4-59
Mean	19.08±13.25	18.08±12.60	22.8±15.36
Gender			
Male	10(40%)	10(40%)	11(44%)
Female	15(60%)	15(60%)	14(56%)

Total 55 (73.33%) patients resided in urban areas, whereas 20 (26.67%) were residents of rural areas (Figure 2). Additionally, more than half of the cases had their onset of disease in autumn and spring (Figure 3).

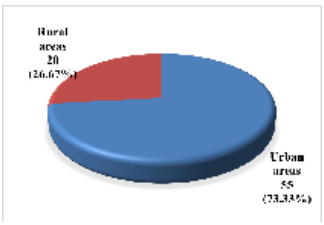

Figure (2): Distribution of PR cases in Urban and Rural areas

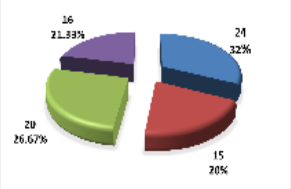

Figure 3: Distribution of PR cases according to the season's onset.

No family history of PR was reported among patients at the time of presentation. With respect to the type of PR, most patients had classical rash (84%), whereas about 16% of patients were presented with atypical forms of PR (Table 2).

Table 2: Distribution of cases according to clinical types of PR.

Type of PR	No. of Cases	Percentage (%)
Classical	63	84
Atypical	12	16
Generalized	4	33.33
Inversed	2	16.67
Double Herald	2	16.67
Localized	1	8.33
Vesicular	1	8.33
EM- Like	1	8.33
Irritative	1	8.33
Total	75	100

Total 28% patients (n=21), in the present study had history of pruritus. Regarding therapeutic outcomes, among the patients who received erythromycin, 76% of them (n=19) showed the best results with complete clearance of the rash by the end of fourteen days. Whereas, prednisolone was found less effective but better than placebo (Table3). The results of follow up at the end of 4th and 6th weeks are shown in Tables 4 and 5 respectively.

Table 3: PR rash clearance at the end of two weeks.

Group	Cleared/Total	%	Chi-square (x^2)	P-value
Erythromycin	19/25	76	20.36 7.95	0.0000064* 0.005†
Prednisolone	9/25	36	3.87	0.05 **
Placebo	3/25	12	21.55	0.00002***

*Erythromycin & Placebo
**Prednisolone & Placebo
†Erythromycin & Prednisolone
*** Erythromycin, Prednisolone & Placebo

Table 4: PR rash clearance at the end of four weeks.

Group	Cleared/Total	%	Chi-square (x^2)	P-value
Erythromycin	22/25	88	20.36 4.99	0.0000064* 0.025†
Prednisolone	15/25	60	6.52	0.01**
Placebo	6/25	24	21.04	0.000027***

*Erythromycin & Placebo
**Prednisolone & Placebo
†Erythromycin & Prednisolone
*** Erythromycin, Prednisolone & Placebo

Table 5: PR rash clearance at the end of six weeks.

Group	Cleared / Total	%	Chi-square (x^2)	P-value
Erythromycin	25/25	100	8.67 2.45	0.0016* 0.1†
Prednisolone	21/25	84	2.55	0.11**
Placebo	16/25	64	11.35	0.0034***

*Erythromycin & Placebo
**Prednisolone & Placebo
†Erythromycin & Prednisolone
*** Erythromycin, Prednisolone & Placebo

The mean duration of PR rash from the start of the treatment to the total disappearance of the lesions was 16.32 ±8.74 days in erythromycin group, 26.8±14.69 days in prednisolone group and 38.8±14.29 days in placebo group (Table 6).

Table 6: Average number of days for PR rash to clear.

Therapeutic group	Mean duration of rash	ANOVA (F-test), p-value
Erythromycin	16.32±8.74	
Prednisolone	26.8±14.69	19.12,
Placebo	38.8±14.29	0.0000001

Regarding the effectiveness of treatment in each group, the patients who were presented within the 1st week of rash appearance and who received erythromycin, their rash was cleared in 14.3±9.4 days. On the other hand, those who were presented within 8-14 days, their rash got disappeared within 18.34±8.44 days. While in prednisolone group, the rash required 26.3±15.37 days to clear if treated in the first week whereas it needed 27.3±14.1 days to disappear if treated in the second week. Regarding placebo group, those who presented in the first week of their disease, the rash abolished in 36.7±14.56 days, while those who were presented in the second week, their rash took 40.9±14.2 days to get cleared (Table 7). Moreover, no significant side effects were reported in any of the therapeutic groups.

Table 7: Average number of days for illness to clear according to time of treatment commencement.

Therapeutic Group	No. of days (treatment started in 1st week)	No. of days (treatment started in 2nd week)	Total
Erythromycin	14.3±9.4	18.34±8.44	16.32
Prednisolone	26.3±15.37	27.3±14.1	26.8
Placebo	36.7±14.56	40.9±14.2	38.8

Discussion

This study was designed to assess two therapeutic agents (erythromycin and prednisolone) in cutting short the duration of PR. The ages of study participants ranged from 3-59 years with second decade as the most common age group. This age group is in accordance with a study which showed that top incidence of this disease occurs in between 10-35 years old patients.[11] Female:male proportion in current study is 1.42:1 which coincides with other studies,[7,8] whereas there are studies which found equal

sex ratio.[10] Another study reported female to male ratio in this disease as 1:2.2-3.[58] Clinically, PR was found in only 28% of cases under study, whereas in another study, the disease was found in 75% of patients.[1] With respect to the clinical types of PR, the classical variety was the most common (84%) which is somewhat similar to a study which reported about 80% of cases as classical.[11]

Despite the cause of PR is not completely known, many studies have reported the use of antibiotics in the treatment of PR for e.g., erythromycin,[39,58] clarithromycin,[42] azithromycin,[38] and doxycycline.[43] These antibiotics have anti-inflammatory and immunomodulatory effects which modify the course of the disease.[7] In present study, erythromycin was given to patients for two weeks and it was found that 19 out of 25 (76%) patients were cleared at the end of two weeks as compared to those in placebo group P=0.0000064). Similarly, significant results were obtained at the end of fourth (P=0.0000064) and sixth week (P=0.0016). The average number of days for PR to be cleared in erythromycin treated patients was 16.32±8.74 days which is highly significant in comparison with prednisolone-treated and placebo-given patients (P=0.0000001). These findings regarding the effectiveness of erythromycin in clearing the rash of PR are in accordance with a study in which 73.3% patients showed complete response with erythromycin[58]

Clarithromycin, a macrolide with a similar action as of erythromycin, has been reported to fully cure the PR patients at the end of 28 days.[42] The results of present study regarding erythromycin coincide with previous studies[42,58] and may indicate its effectiveness in reducing the duration of the rash in PR patients. However, there are studies which oppose these findings.[39,48]

Another antibiotic doxycycline has been investigated in an Iraqi placebo-controlled study where 65.2% of the patients who were given this antibiotic showed an excellent response i.e. 75% of their rash got disappeared.[43] These results coincide with findings of present study taking into account the effectiveness of the antibiotics in PR therapy.

Although virological cause of this disease has been documented by many studies,[13-15] it is still not confirmed yet.[59-61] Similarly, microbial incrimination has also been disapproved by many studies.[12,62-65] Therefore, prednisolone is also investigated in this study in treatment of PR based on that it might be a hypersensitive or reactionary condition. The results revealed it to be better than placebo with a significant statistical difference (P=0.05) but less effective than erythromycin (P=0.005).

The information about the usage of oral corticosteroids in the treatment of PR is scarce, however, few studies have recommended the use of systemic corticosteroid for the widespread, severe and recalcitrant forms of PR.[34,66] In contrast, a study reported that it may exacerbate PR and even cause erythroderma.[56] Whereas in present study, prednisolone was found effective in PR and no exacerbation of PR was encountered in any of the patients.

Timing of initiation of treatment, whether it has been started within the first week or the second week, showed minor impact on the course of PR in all study groups (p-value=0.26, 0.87 and 0.47 for erythromycin, prednisolone and placebo group respectively). These results may be attributed to the limited number of cases recruited in this study. Regarding the side effects, no patient encountered any significant unwanted effects during the period of treatment, and this goes in parallel with a study which used erythromycin,[58] however contrasting results were observed with prednisolone in a study.[56]

Conclusions and Recommendations

1. Although both oral erythromycin and prednisolone are effective drugs in shortening the course of PR; yet, erythromycin is superior to prednisolone.
2. The use of both oral erythromycin and prednisolone in recommended doses and duration in this study showed no significant side effects.
3. A larger scale study is recommended to assess the effectiveness of erythromycin and prednisolone in higher doses in treatment of PR.

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