Azathioprine versus betamethasone for the treatment of parthenium dermatitis: A randomized controlled study

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ABSTRACT

Background: *Parthenium hysterophorus* is the commonest cause of airborne contact dermatitis in India. Azathioprine has been shown to be effective and safe in parthenium dermatitis, but there are no reports of comparison of steroids and azathioprine in this condition. **Aims:** To study the therapeutic efficacy of azathioprine versus betamethasone in patients having contact dermatitis to parthenium and compare the side effects of the drugs. **Methods:** Fifty-five patients of airborne contact dermatitis to parthenium were randomly assigned to treatment with azathioprine 100 mg daily (group A) or betamethasone 2 mg daily (group B), for 6 months in a blinded manner. The patients were evaluated every month for 6 months to determine the response to treatment and side effects and then further followed up for another 6 months to determine any relapse. **Results:** There were 26 patients in group A and 29 in group B, of which 20 patients of group A and 21 of group B completed the study. Nineteen (95%) patients in group A and all 21 (100%) patients in group B had an excellent response (complete remission) to treatment ($P = 0.0156$ *vs.* 0.0005). The patients in group B, however, had more adverse effects (Fisher exact, $P \leq 0.05$). Nine (45%) patients in group A and 14 (67%) patients in group B relapsed during the post-treatment follow-up. **Conclusions:** Azathioprine and betamethasone appear to be almost equally effective ($P = 0.0156$ *vs.* 0.0005) in the treatment of parthenium dermatitis. However, adverse effects and relapses were observed to be more frequent in patients treated with betamethasone.

Key Words: Azathioprine, Betamethasone, Parthenium dermatitis, Side effects, Treatment

INTRODUCTION

Parthenium hysterophorus is the commonest cause of airborne contact dermatitis, also known as parthenium dermatitis (PD), in India. PD has become one of the major dermatological problems in our country.[1,2] Though it has very low rate of mortality, the disease usually persists with variable remissions and relapses, causing great distress and morbidity. Corticosteroids have been the mainstay of treatment for PD.[2] These patients require corticosteroids for prolonged periods due to chronicity of the disease and tend to develop severe and sometimes irreversible side effects of corticosteroids.[3,4] Azathioprine is an immunosuppressive drug which acts by inhibiting the T lymphocytes.[5] In our previous studies, we have demonstrated that azathioprine is effective[6,7] and safe even on long-term use in PD.[8] We could induce long-term remissions with azathioprine in these patients. However, there are no studies comparing the efficacy of azathioprine with that of corticosteroids in parthenium dermatitis. We therefore studied the therapeutic efficacy of azathioprine versus betamethasone in patients having contact dermatitis to parthenium and evaluated the side effects of the drugs both clinically and biochemically.

METHODS

Patients with a clinical diagnosis of parthenium dermatitis attending the skin outpatient of our hospital between

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February 2003 and September 2004 were taken up for the study. The study was approved by the Institutional Ethical Board. Patients below the age of 18 years; pregnant and lactating women; and patients with abnormal baseline hematological, liver, or renal function tests were excluded. A written informed consent was taken from all the patients. A random allocation sequence was generated by a faculty colleague not associated with the study using the random number table. Identical sealed brown paper packets containing either 60 tablets of azathioprine (50 mg) or 60 tablets of betamethasone (1 mg) were numbered according to the allocation sequence. Patients were randomly assigned to treatment with azathioprine (group A) or betamethasone (group B), 1 tablet twice daily for 6 months in a blinded manner. Antihistamines (cetirizine hydrochloride, 10 mg) once daily orally and clobetasol propionate (0.05% w/w) cream topically were given to all the patients for symptomatic relief in the beginning. No other drugs, including medicines of alternative systems, were given. The patients in both the groups were advised to use protective clothing and to frequently wash the exposed areas with soap and water, in addition to the specific intervention.

A detailed clinical evaluation was undertaken in each patient. The severity of the disease was assessed by determining the clinical severity score (CSS) on the basis of (a) itching, (b) morphology of skin lesions, and (c) areas of involvement. Itching and morphology were graded on a scale of 0 to 3, i.e., itching was graded as 0 - no itching; 1 - mild itching; 2 - moderate itching; and 3 - severe itching. Similarly morphology was graded as 0 - no lesions; 1 - papules; 2 - plaques; and 3 - lichenified plaques. The areas of involvement, however, were graded on a scale of 1 to 4, i.e., 1 - only face; 2 - face, neck, and hands; 3 - all exposed sites and flexures; and 4 - erythroderma. The final score was calculated by adding the individual scores for a, b, and c and multiplying by 10, viz., $(a+b+c) \times 10$, to get a maximum score of 100. The patch test with standardized aqueous extract of the plant antigen[9] was done to confirm the diagnosis in each patient. Tenfold aqueous dilutions of the standard extract varying from $1:10^1$ to $1:10^5$ were used to determine the titer of contact hypersensitivity (TCH).[10] The maximum dilution which produced a definite dermatitic reaction in the patient was taken as the TCH in that patient. Laboratory investigations consisting of hemoglobin, total blood count, differential count, platelets, serum bilirubin, serum alkaline phosphatase, serum transaminases, serum electrolytes, blood sugar (fasting and postprandial), serum creatinine, blood urea, urine routine and microscopy, stool examination for occult blood, chest X-ray, and electrocardiogram (ECG) were carried out before starting the therapy. Blood pressure and weight were recorded, and clinical photographs of each patient were taken. The estimation of thiopurine methyltransferase (TPMT) enzyme activity was not done due to lack of facilities.

Clinical evaluation was undertaken every month to determine the CSS. At each visit, severity of itching, erythema, flattening of the lesion, healing of the lesions, occurrence of new lesion if any, and the overall improvement were also determined. The patients were evaluated for side effects too. Their blood pressure and weight were also recorded at each visit. After 6 months, the treatment was stopped and an overall evaluation was done to determine the response to treatment in each patient in either group. Post-treatment photographs were also taken to evaluate the treatment response. The response was considered to be excellent if the overall improvement was 75% to 100%; good, if it was 50% to 75%; and poor, if it was below 50%.

All the pre-treatment investigations except chest X-ray, ECG, and TCH were repeated every month during the study period to determine any abnormalities in these tests. Chest X-ray, electrocardiogram, and TCH were, however, repeated every 3 months to determine any change.

The patients in both the groups were followed up every month for 6 months after stopping the treatment to determine any relapse of the disease. The disease was considered to have relapsed if the CSS increased to more than 50% of the pre-treatment level.

RESULTS

A total of 55 patients, 41 males and 14 females, between 24 and 73 years of age (mean, 45.94 years) having disease for 1 to 34 years (mean, 5.48 years) were enrolled in the study. Of these, 41 patients, 29 males and 12 females, completed the treatment. There were 20 completed patients in group A and 21 in group B [Figure 1]. Fourteen patients (6 in group A and 8 in group B) were lost to follow-up. Of these, 4 patients could not continue treatment due to various reasons i.e. 2 patients did not come for follow-up due to long traveling distance, 1 switched over to an alternative system of medicine, and 1 died due to an acute gastrointestinal problem in another hospital (details were not available) respectively. The reasons for not following up were not known in the remaining patients.

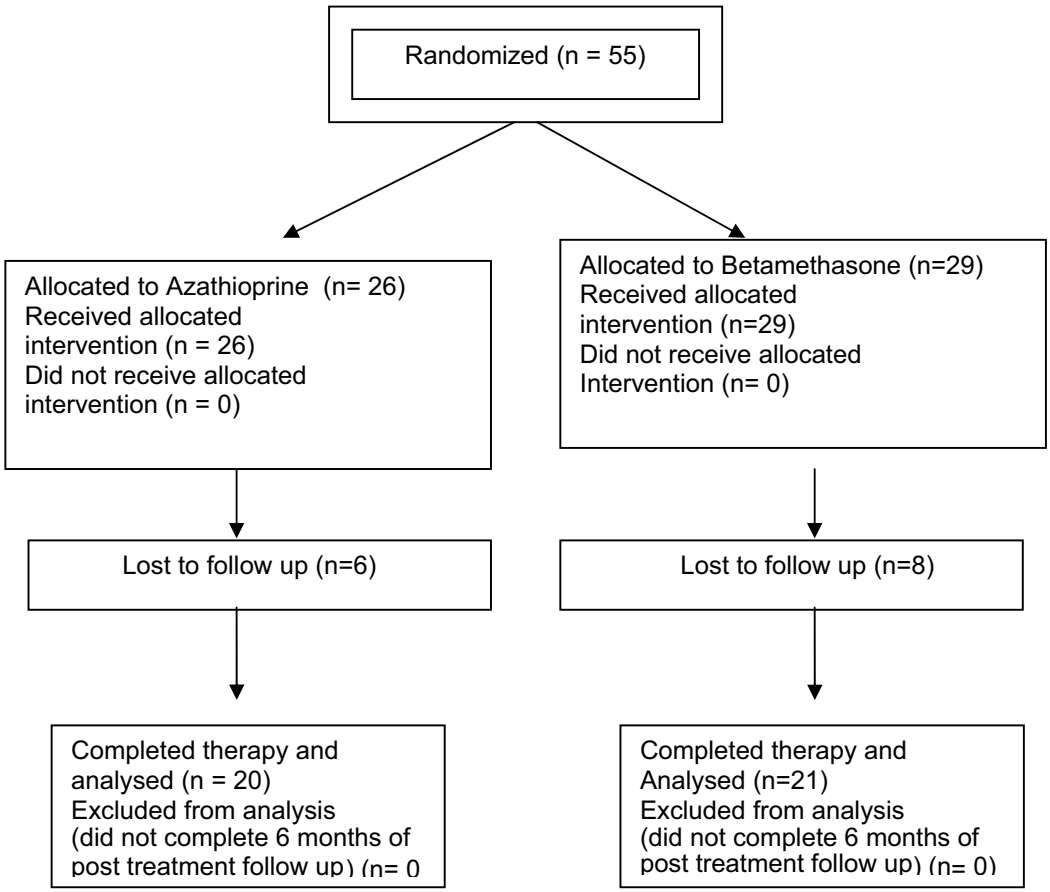

Figure 1: Randomization, allocation and analysis of the patients

Response to treatment

A total of 20 patients (13 males and 7 females, between 25 and 60 years of age [mean, 48.5 years], having the disease for 2 to 34 years [mean, 7.23 years]) in group A; and 21 patients (16 males and 5 females, between 26 and 73 years of age [mean, 50.7 years], having the disease for 1 to 12 years [mean, 5.21 years]) in group B completed the study. Nineteen (95%) patients in group A and all 21 (100%) patients in group B had excellent response to the treatment [Table 1], within a mean 3.6 and 2.9 months respectively, after initiation of treatment. One patient in group A had poor response. The mean pre-treatment CSS decreased from 64.5 ± 16.37 to 4.3 ± 5.57 (P = 0.0156) in group A, while it decreased from 67.14 ± 17.36 to 0.59 ± 2.22 (P = 0.0005) in group B [Figure 2].

Table 1: Response to treatment

Response	Number of patients	
	Group A	Group B
Excellent	19 (95%)	21 (100%)
Good	0	0
Poor	1	0
Total	20	21

Titer of contact hypersensitivity

The TCH became negative in 8 patients, decreased in 6, remained unchanged in 5, and increased in 1 patient in group A; while it became negative in 9 patients, decreased in 11, and remained unchanged in 1 patient in group B.

Adverse effects

Adverse events were noted in both the groups [Table 2].

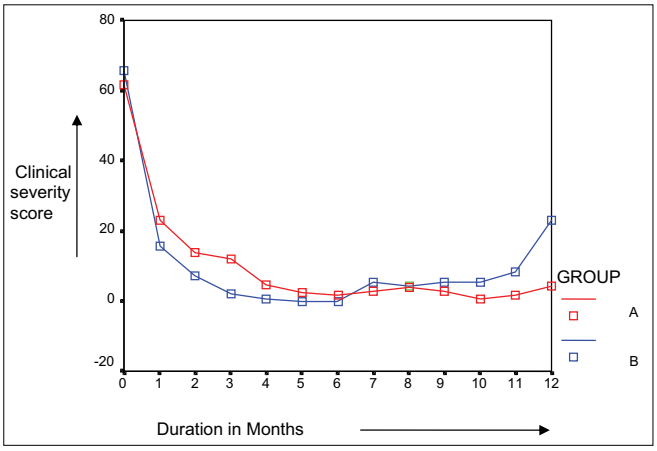

Figure 2: Comparison of efficacy between the two groups

Table 2: Side effects in patients of the two groups

Side effect	Group A (n=20)	Group B (n=21
Acne	-	7 (33) *P* = 0.009
Straie	-	6 (28) *P* = 0.021
Cushingoid features	-	5 (23) *P* = 0.048
Hirsutism	1 (5)	3 (14)
Dyspepsia	5 (25)	7 (33)
Nausea/vomiting	3 (15)	1 (4.8)
Weight gain	3 (15)	10 (47) *P* = 0.043
Diabetes mellitus	-	1 (4.8)
Cataract	-	1 (4.8)
Glaucoma	-	1 (4.8)
Hypertension	-	5 (23.8) *P* = 0.048
Infections		
Bacterial	8 (40)	9 (42.9)
Viral	1 (5)	1 (4.8)
Fungal	6 (30)	7 (33)
Pigmentation	-	2 (9.5)
Backache	3 (15)	4 (19)
Fever	5 (25)	3 (14.3)
Loss of appetite	7 (35)	7 (33)

Figures in parentheses are in percentage

Acne, striae, Cushingoid features, weight gain and transient rise in blood pressure were more frequent in group B; this difference was statistically significant (Fisher exact, ≤0.05). However, there was no statistically significant difference in other adverse effects. The adverse effects did not warrant stoppage of therapy in any of the patients and were managed appropriately. All the hematological and biochemical parameters remained within the normal range. There were no abnormalities detected in urine and stool examinations, X-ray chest, and ECG evaluations during the study period.

Relapse

Twenty patients in group A and 21 patients in group B completed 6 months' post-treatment follow-up. Nine (45%) patients in group A and 14 (67%) patients in group B had a relapse, which was statistically not significant ($P > 0.05$) between the groups. The disease relapsed after 1, 2, 3, and 4 months in 3, 2, 1, and 3 patients respectively in group A; while it relapsed after 1, 2, 3, 4, 5, and 6 months in 2, 3, 4, 1, 2, and 2 patients respectively in group B. Eleven patients in group A and 7 in group B did not have any relapse during this period.

DISCUSSION

Corticosteroids are the mainstay of treatment in parthenium-induced dermatitis.[1,2] Since it is a chronic disease with exacerbations usually in summer and monsoons, these patients require corticosteroids for prolonged duration. Regular intake of corticosteroids for prolonged periods is often associated with severe and sometimes irreversible systemic side effects[3,4] like osteoporosis, osteonecrosis, growth retardation, myopathy, posterior subcapsular cataracts, open angle glaucoma, neuropsychiatric symptoms, epidural lipomatosis, hyperglycemia, weight gain, Cushingoid facies, hypocalcemia, hypokalemic alkalosis, hypertension and atherosclerosis, predisposition to infections and reactivation of tuberculosis, hypothalamo-pituitary-axis suppression, etc.

Azathioprine has been shown to be an effective corticosteroid-sparing agent in the treatment of parthenium dermatitis.[6,7] It is a 6-mercaptopurine derivative, which inhibits purine synthesis and acts as a potent immunosuppressive and a powerful anti-inflammatory agent. Its immunosuppressive effect is owing to inhibition of the activated T-lymphocytes,[5] the cells which are primarily responsible for the dermatitis. The drug has been shown to be safe even on long-term use, without any significant side effects.[8] Rarely, however, it may cause hepatotoxicity and myelosuppression.

In this double-blind randomized controlled study, the response to treatment with azathioprine and betamethasone was compared. Nineteen (95%) patients in azathioprine group (group A) and 21 (100%) in betamethasone group (group B) had excellent response [Table 1]. The mean pre-treatment CSS in group A decreased from 64.5 ± 16.3 to 4.3 ± 5.57 ($P = 0.015$). In group B, however, it decreased from 67.14 ± 17.36 to 0.59 ± 2.22 ($P = 0.0005$) [Figure 2]. In both the groups, the decrease in CSS was statistically highly significant. The patients in group B were observed to have betamethasone-induced side effects like acne, striae, Cushingoid features, weight gain, etc., which were statistically significant (Fischer exact, ≤0.05) [Table 2]. But none of these side effects were significant enough to warrant stoppage of therapy in any patient. The patients in azathioprine group did not have significant side effects, as has been reported in other studies also.[7,8] There were no significant changes in titer of contact hypersensitivity in either group after treatment. In our previous study also, we could not demonstrate any correlation between TCH and severity of the disease or response to treatment.[11] Laboratory parameters also remained within normal range in all the patients. We did not do TPMT estimation in our patients because of lack of facilities. Moreover, it has been shown that the prospective estimation of TPMT enzyme activity does not predict azathioprine-induced adverse effects.[12]

Nine (45%) patients in group A and 14 (67%) in group B relapsed during the follow-up. The relapse rate was statistically not significant ($P > 0.05$) between the groups. The remaining patients remained in remission during this period.

The study has therefore shown that azathioprine and betamethasone are equally effective in the treatment of parthenium dermatitis. However, betamethasone produced significant adverse effects. We therefore concluded that azathioprine can be used as an effective and safe alternative drug for the treatment of parthenium dermatitis. However, our study suffers from the following limitations. Apart from having a small sample size the exact amount of topical clobetasol propionate used by each patient was not determined, which probably could have varied in different patients. However, since the mean pre-treatment CSS, which were 64.5 ± 16.3 in group A and 67.14 ± 17.36 in group B, were comparable, the patients in both the groups are likely to have used roughly comparable amount of the drug, which may have affected the results equally in both the groups. Larger studies, however, are recommended to confirm our results.

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