

Research Article

Single Blind Randomized Controlled Trial of 'Azathioprine Versus Corticosteroids in *Parthenium Hysterophorus* Induced Contact Dermatitis'

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Abstract

Parthenium dermatitis is a common physically, psychologically and financially debilitating condition faced mostly by farmers in certain parts of India, especially the northern belt of Karnataka.

Aim

To study the effectiveness of Azathioprine and corticosteroids in patients with *Parthenium hysterophorus* induced airborne contact dermatitis and to monitor side effects and duration of relapse.

Materials and Methods

34 patients with Parthenium induced air-borne contact dermatitis, diagnosed clinically and proven by positive patch tests with Parthenium were included and randomized into 2 groups of 17 each, the first receiving 100 mg Azathioprine daily for 6 months, and the other 30 mg Prednisolone in tapering doses for 2 months and placebo for 4 months. Disease activity, itch and sleep loss were scored and monitored.

Result

In the Azathioprine group, six out of 7 patients who completed treatment showed more than 50% improvement after 3 months of treatment with a longer remission lasting from 2-15 months, whereas in Prednisolone group, 8 out of 13 people who completed treatment showed significant improvement but relapsed on stopping treatment. Severe side effects were not seen in both groups.

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Conclusion

Azathioprine gives lasting results, a stable prolonged relapse free period and is suitable for a chronic problem like Parthenium dermatitis, but has to be used with caution with proper monitoring. Prednisolone is ideal for acute severe flare ups as a short course therapy, with an early withdrawal for avoiding associated morbidities.

Keywords: Air Borne; Azathioprine; Contact Dermatitis; Oral Prednisolone; Parthenium

Introduction

Contact dermatitis is an allergic response of the skin to a surface contactant. Sometimes individuals develop contact dermatitis to suspended air particles, without a direct contact. The allergic dermatitis caused thus is termed as Air Borne Contact Dermatitis (ABCD). In India, *Parthenium hysterophorus*, commonly called as Congress grass is a common cause for ABCD. It is a weed of the Compositae family which got introduced into India with the imported wheat grains from Texas and was first identified in 1956 in Pune and has been a menace since then [1]. ABCD to *Parthenium hysterophorus* is a major problem in certain parts of India and is comparable to poison oak and poison ivy dermatitis in European countries. Apart from dermatitis, there is associated photosensitivity and no treatment has resulted in complete cure.

So far, corticosteroids along with other measures like protection from antigen, photoprotection, frequent washing of exposed area and removing the plant from area of residence, has been the mainstay of treatment. Prolonged corticosteroid intake in a chronic though, benign disease may lead to various serious and even life-threatening systemic side effects. Azathioprine is a 6-mercaptopurine derivative which inhibits purine synthesis and acts as an immunosuppressive and a powerful anti-inflammatory agent [2]. It inhibits T helper cells which are primarily responsible for the dermatitis in ABCD and has been successfully tried in Chronic Actinic Dermatitis (CAD) [3]. Effectiveness of Azathioprine in the treatment of ABCD from sesquiterpene lactones has been reported [4]. In earlier preliminary studies we have found that 50-100 mg oral daily dose of Azathioprine induces a clinical remission without significant clinical or biochemical side effects in patients with ABCD to Parthenium [5,6].

This study is undertaken to compare the efficacy of azathioprine with that of corticosteroids, and to evaluate the side effects.

Aims

1. To study the effectiveness of azathioprine and corticosteroids in patients with *Parthenium hysterophorus* induced airborne contact dermatitis.
2. To monitor the side effects of the drugs both clinically and biochemically.

Materials and methods

A Single blinded randomized clinical trial, recruiting patients with clinically and patch test proven Parthenium dermatitis, over a period of two years with one year follow up of all patients.

Inclusion criteria

1. All patients with Parthenium induced air-borne contact dermatitis, diagnosed clinically and proven by positive patch tests with Parthenium.
2. Age group 20 to 80 years.

Exclusion criteria

1. Women in childbearing age group who have not completed their family.
2. Pregnancy and lactation.
3. Patients with gastrointestinal problems like gastritis, peptic ulceration, hiatus hernia, liver or renal impairment.
4. Patients whose baseline investigations revealed hematological abnormalities of liver or renal function.
5. Patch test positivity to allergens in the Indian Standard Series (ISS).
6. Intake of other drugs likely to affect the disease, e.g., medicines of alternate system.

Randomization procedure

The two treatment groups A and B (Azathioprine group and corticosteroid group) were selected using computerized random number table.

Procedure: All clinically diagnosed patients were patch tested with Parthenium antigen, 0.5% and 1% in petrolatum. The antigen was prepared from freshly collected Parthenium plant in the Department of Pharmacognosy, College of Pharmaceutical Sciences (COPS), Manipal, Karnataka and India. The plant identification and confirmation was done by experienced taxonomist. Solid-liquid extraction technique by Soxhlet extraction method was used to make the patch test antigen. Dilutions of 0.5% and 1% of the extract in petrolatum were prepared.

Treatment procedure: Thirty four severely affected patients with features of Parthenium dermatitis, patch tested positive for Parthenium (and other allergens excluded by patch test) and satisfying the inclusion criteria were taken for the study. Detailed history was noted on the proforma after an informed content. Basic investigations included complete haemogram, urine and stool routine examination, fasting and postprandial blood sugars, renal and liver function tests, serum electrolytes, chest radiograph and ECG.

After randomization, Group A received Azathioprine 50 mg twice daily for 6 months and group B, prednisolone in tapering doses of 30 mg for 2 weeks, 20 mg for 2 weeks, and 10 mg for 4 weeks, thereafter oral placebo for next 4 months. The side effects were monitored at monthly intervals. After 6 months, the patients were followed up for the next 6 months. Antihistaminics (pheniramine maleate 25 mg twice daily) were given based on need.

- The patients on steroids were given antacids. All patients were given topical betamethasone valerate once daily.
- Clinical assessment was undertaken monthly for 12 months.
- Disease activity was evaluated using Dermatitis Assessment Severity Index (DASI).
- Itch was scored on a Visual Analogue Scale (VAS) 0-100 mm recorded graphically.
- Sleep loss was recorded in percentage graphically.

All patients were evaluated for side effects of Azathioprine and corticosteroids clinically as well as by laboratory parameters as given in the protocol at 3 monthly intervals.

General management: In addition, patients in both groups were advised use of protective clothing and avoidance of sun; frequent washing of exposed areas and application of topical steroids and oral administration of antihistaminics if itching was severe.

Patients who developed side effects of the drug were given standard out or in patient care as appropriate. Patients who developed an exacerbation of their disease while on study were withdrawn and given other appropriate therapy to control the disease.

Statistical analysis: was done using chi-square test, paired samples test, independent samples test and nonparametric tests.

Results

A total of 34 patients, 30 males and 4 females, ages ranging from 20-80 years were enrolled in the study and randomized in 2 groups of 17 each to receive Azathioprine and prednisolone, respectively. Majority were in 5th to 7th decades, maximum being in the 6th decade (Chart 1).

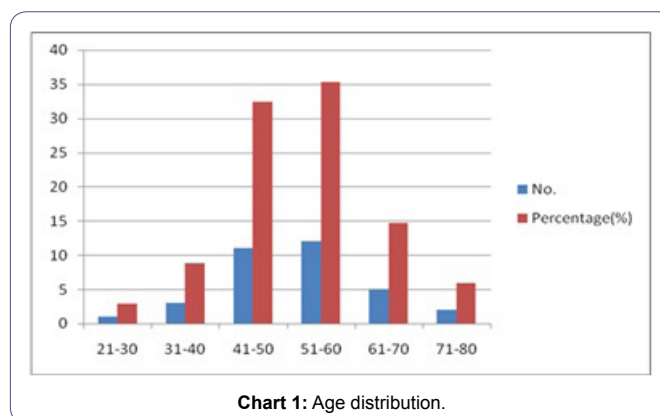


Chart 1: Age distribution.

Agriculturists were the maximum affected (64.7%), followed by manual laborers and house wives. All the patients were from various districts of Karnataka state, most of them from Davangere (12 patients, i.e., 35.3%), where Parthenium is rampant. 16 patients (47%) complained of aggravation in summer, followed by 5 patients (14.7%) who had aggravation in winter.

Twenty-eight patients (82.4%) gave history of direct contact with the plant. Thirty-two (94.1%) had history of exacerbations and remissions. A very significant number of patients (32, i.e., 94.1%) gave history of photo aggravation. Two patients (5.9%) had atopic background in the form of allergic rhinitis and family history of asthma. The most common associated disorders observed were diabetes mellitus in 6 (17.65%) and hypertension in 5 (14.7%). There were 12 smokers, 8 people who consumed alcohol and 4 betel nut chewers, but none attributed their aggravation to their habits. Previous treatment modalities: Majority were treated with topical steroids. (28 patients, i.e., 82.4%), antihistamines (67.7%) and systemic steroids (41.2%). Other modalities included emollients, azathioprine, ayurvedic and homeopathic medicines, sunscreens and hydroxychloroquine.

The most common pattern of presentation in this study was that of ABCD type in 31 patients (91.2%) involving photoexposed areas plus

eyelids, ear creases, naso-labial folds, retro-auricular area, cubital and popliteal fossae.

Other presentations included photo dermatitis in 3 patients, Actinic reticuloid in 2 and hand dermatitis in one (Table 1).

Pattern	Number (n=34)	Percentage (%)
ABCD	31	91.2
Photodermatitis	3	8.8
ABCD with hand dermatitis	1	2.9
ABCD with lichenoid pattern	1	2.9
CAD/Actinic Reticuloid pattern	2	5.9

Table 1: Pattern of dermatitis.

Extent of involvement

In majority, the lesions were disseminated and varied from erythematous papules, nodules, plaques, erosions, lichenification, hyperpigmentation, oozing and secondary infection. The extent of involvement varied from 10-80% and sun exposed sites were predominantly affected.

Treatment

Only seven patients (41.2%) completed the six month treatment in the Azathioprine group (n=17), whereas 13 patients completed the two months treatment in the prednisolone group. (n=17) (Table 2).

Group	Completed	Dropped out
Azathioprine (n=17)	7 (41.2%)	10 (58.8%)
Prednisolone (n=17)	13 (76.5%)	4 (23.5%)

Table 2: Treatment groups.

In the Azathioprine group, one patient (14.3%) had complete remission at the end of six months, 5 patients (71.4%) had significant improvement and one patient (14.3%) initially improved, later worsened. Six out of 7 patients who completed treatment showed more than 50% improvement after 3 months of treatment (Table 3).

The patient with complete remission did not relapse even after 6 months of follow up. One patient relapsed 18 months after stopping treatment and another relapsed within 2 months. An average of 2-18 months of relapse free period after stopping Azathioprine treatment was observed in this study. Clinical response to Azathioprine was visible by 2 months in all patients. All experienced mild worsening of dermatitis on exposure to sunlight and outdoor work. In the prednisolone group, out of 13 patients who completed the treatment, 8 had significant improvement (Table 3).

Percentage of reduction in DASI	Azathioprine group		Prednisolone group	
	No. (n=7)	Percentage (%)	No. (n=13)	Percentage (%)
Complete remission (100%)	1	14.3	3	23.07
80-90%	3	42.9	3	23.07
50-80%	2	28.6	2	15.4
Initial improvement followed by worsening	1	14.3	5	38.5

Table 3: Percentage of reduction in DASI after treatment in Azathioprine group.

Side effects

The most common side effects with prednisolone were gastrointestinal side effects, viz., loss of appetite, heart burns, dyspepsia, pain abdomen, nausea, vomiting. Others were insomnia, secondary infections, weight gain and facial puffiness. There was no increase in blood sugars or pressure or other side effects. This may possibly be due to the relatively low dose of prednisolone started (30 mg per day) and the relatively rapid taper within a period of 2 months. Azathioprine was well tolerated, except for two. One patient who had ABCD developed anemia, jaundice and multiple furuncles and the other developed anemia and cellulites. In both, Azathioprine was stopped and oral steroids started.

Statistical analysis

As sample sizes were small, there was no significant difference in p-value in case of DASI before and after treatment in Azathioprine group. (p=0.134). The paired samples test showed significant p-value in DASI before and after prednisolone treatment (p=0.010). Non parametric tests were done using Mann-Whitney test, which again showed insignificant p values in cases of DASI, itch and sleep in both groups.

Discussion

Parthenium dermatitis is now rampant in India, especially in pockets in the north and southwest. It usually affects adult males, earlier studies showing a male: female incidence of 4.55:1 [7]. Our study showed a ratio of 7.5:1, probably because women tend to remain indoors more often, reducing the risk for exposure and sensitization. The influence of age in the study was striking, the maximum number of affected cases being in the group of 41-60 years, unlike other studies which observed 30-39 years [7]. The duration of the disease in this study ranged from 6 months to 20 years which shows the chronic nature of Parthenium dermatitis. Majority of the affected patients were invariably exposed to the allergen most of the times and the severity of the dermatitis depends not only on irritant or allergic potential of the plant, but also on degree of exposure and individual sensitivity. The principle source of exposure was direct contact with the living plant. The plant hairs (trichomes) contain surplus of dermatitis producing sesquiterpene lactones. The airborne pollen also contains the oleoresin leading to ABCD. The plants crumble during summer season to a finely scattered dust, which virtually fills the surrounding atmosphere and forms another source of ABCD [8]. Lack of sun protection, working and hygienic habits may also contribute to chronicity of the disease. Clothes dried outside in sun may also act as a potential trap for airborne Parthenium allergens and on sweating the allergens leach out on to the skin to produce a chronic recurrent dermatitis. One of our patients had onset of dermatitis following wearing a shirt which was kept to dry in open air on a Parthenium plant.

Most complain exacerbation in summer, may be due to sweating as well as photosensitive nature of the plant. Photo contact dermatitis to Parthenium has been reported earlier [9], but we were unable to prove it as the Parthenium antigen showed equal reactions on irradiated as well as non-irradiated sites on photo patch testing (unpublished observation). Exposure to airborne plant allergens may first cause ABCD which mimics photo dermatitis, but subsequently develop true photo dermatitis like Chronic Actinic Dermatitis (CAD) or Actinic Reticuloid (AR) syndrome.

Earlier studies have shown that reduction of MED to UVB is a definite indicator of photosensitivity in Parthenium dermatitis [10]. It is possible that retention of photo allergen at site of repetitive photoallergic reactions can cause classic photo allergic reactions with photo antigen trapped in the skin; the reactions lasting for months to years. Majority of our patients were middle to old aged, hence explaining the long term influences of the allergen.

Major aggravating factors in this study were the 3 'S's - sunlight, summer and sweating. 82.2% had direct contact with the plant during their work, and the rest may have developed the disease due to the air borne nature of Parthenium dermatitis.

The various patterns of dermatitis we observed were airborne contact dermatitis, photo dermatitis, hand dermatitis, lichenoid and chronic actinic reticuloid pattern.

Frequent concurrence of atopic dermatitis with Compositae dermatitis has been reported in some earlier studies [11], but not in our study. Increased incidence of Parthenium dermatitis in atopics may be due to the chronically irritated and damaged skin which makes them susceptible to sensitization of any nature.

The efficacy of Azathioprine in Parthenium dermatitis has been shown earlier, so also its relapsing tendency on stopping medication [6,12]. Azathioprine is a 6-Mercaptopurine analogue which acts by interfering with DNA and RNA synthesis and repair. It has a greater effect on T cells than B cells, and also on Langerhans cells, NK cells and monocytes. Azathioprine inhibits the effector phase of immune response, but not the induction phase. The adverse effects include nausea, vomiting, diarrhea, abdominal pain, pancytopenia, hepatotoxicity, pancreatitis, polyneuropathy, drug rash and fever, as well as increased incidence of malignancies, especially in transplant patients on long term treatment.

In the present study, a large number of drop outs (58.8%) in the Azathioprine group may be due to the delay in onset of action and poor control of itch. We were unable to contact the dropouts and enquire the exact reason for the same. Though corticosteroids act faster, Azathioprine has a 'steroid sparing effect' leading to lower dosage of steroids and thus a lesser risk of serious steroid induced adverse effects while maintaining an adequate immunosuppressive effect.

In our study, prednisolone group generally had good initial improvement, but there was no long lasting remission whereas Azathioprine group had relatively better stable disease free period ranging from 2 to 15 months after stopping the drug. The non significance of p-value may be due to the higher number of dropouts in the Azathioprine group. The shorter duration of steroid schedule was safe enough to avoid serious side effects but not adequate enough for prolonged control of the dermatitis. Relapsed patients who were started on oral mini pulse steroid therapy (betamethasone 6 mg weekly once or twice) responded very well with longer remissions and least number of side effects.

The medical management of Parthenium dermatitis will be useless unless the patient is seriously motivated for proper preventive measures. The most effective treatment would be to fully remove the patient from Parthenium infested areas, but as this is impractical in most cases, we need to focus on other points like removal of plant from the patient's environment as far as possible, frequent washing of exposed areas with soap and water before the antigen penetrates the skin, use of barrier cream, frequent changes and washing of used

clothes, limiting sun exposure, drying of washed clothes indoors etc. We are also attempting to devise an acceptable mask to be worn by severely affected people when out in the open.

The statistical significance to confirm the superiority of either of the drugs in terms of improvement in DASI, itch and sleep was undermined by the large number of dropouts in the Azathioprine group, which clinically had an edge over the prednisolone group in terms of prolonged remission. Clinically the beneficial effects of Azathioprine were very obvious, with a progressively steady rise in improvement of scores in all assessment parameters, a stable post treatment period and a better patient compliance. Prednisolone, on the other hand, demonstrated a quicker onset of action, but a quicker relapse as well.

We would like to conclude that Azathioprine gives lasting results, a stable prolonged relapse free period and is suitable for a chronic problem like Parthenium dermatitis, but has to be used with caution with proper monitoring. It is imperative that the patients be counselled regarding the nature of their condition, the slow onset of action of azathioprine and the need for lifestyle changes and proper medication and photoprotection. Prednisolone is ideal for acute severe flare ups as a short course therapy, with an early withdrawal for avoiding the associated morbidities.

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