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A COMPARATIVE STUDY OF WEEKLY PULSE DOSE VERSUS DAILY DOSE OF AZATHIOPRINE IN THE TREATMENT OF PARTHENIUM DERMATITIS

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A B S T R A C T

Background: Parthenium dermatitis is the commonest cause of airborne contact dermatitis (ABCD) in India causing great distress to the patients. Off late, Azathioprine (AZA) in different dosing schedules seems to be effective and safe, but there are only few reports in the literature comparing the weekly and daily dosage of Azathioprine in parthenium dermatitis.

Aims: To study the therapeutic efficacy of Azathioprine weekly pulse (AZA-W) and daily Azathioprine (AZA-D) in the treatment of parthenium dermatitis.

Methods: Twenty-two patch test confirmed patients of ABCD to parthenium were randomly allocated to treatment with 300mg weekly pulse (group A) or daily azathioprine 50 mg (group B) for 3 months. Patients were followed up at the end of each month to evaluate the response by assessing clinical severity score and side effects to treatment.

Results: Out of 22, there were 12 patients in group A and 10 patients in group B. The mean baseline clinical severity score decreased from44.65 ± 12.22 to 13.83 ± 4.84 in group A, and from 42.69 ± 11.56 to 23.34 ± 8.37 in group B, which was statistically significant. Patients on WAP had a higher incidence of side effects and relapse rate was higher in group B.

Conclusion: In this open study, Azathioprine in weekly pulse doses has found to be superior to daily regimen without any serious adverse effects in the treatment of parthenium dermatitis.

INTRODUCTION

Airborne contact dermatitis is the most common allergic contact dermatoses encountered in outpatient clinics. Though ABCD is of multifactorial origin, *Compositae* weed, *Parthenium hysterophorus* is still the leading cause in India.[1] Since the antigens present ubiquitous in the atmosphere, disease usually persists with frequent relapses and remissions and causing great distress to the patient.

Multimodality approach with efforts to control weed, desensitization and protective measures have been tried with inconsistent results.[2,3] Different classes of drugs with long term immune suppression have been used to achieve control of the disease. Systemic corticosteroids were the mainstay of therapy until a safer drug with better therapeutic window, Azathioprine has been emerged. Azathioprine acts by inhibiting the proliferation of T lymphocytes thereby causing imunosuppression.[4]

Various preliminary studies on azathioprine in the treatment of parthenium dermatitis have given encouraging and consistent good results.[5] Hence, this study was conducted to compare the efficacy of weekly pulse and daily dose of azathioprine in parthenium dermatitis.

MATERIALS AND METHODS

This study was conducted in the outpatient department of Dermatology, Venereology and Leprosy, Rajah Muthiah Medical College and Hospital, a tertiary care centre in South India, between November 2016 to October 2018, for a period of two years. Ethical clearance was sought from institutional ethics committee before beginning the study.

Twenty-two cases of Parthenium dermatitis, both old and new, in the age group 25-65 years, confirmed by patch testing, were included in the study after a proper written

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consent. Patch testing was done using Indian standard series supplied by Systopic labs, New Delhi. Patients with active infections, malignancy, hepatic and renal impairment, pregnant ladies were excluded from the study. The patients were randomly divided into 2 groups with group A and group B comprising of 12 and 10 cases respectively.

Detailed history including demographic factors, duration of present episode, seasonal variation and previous treatments were recorded in the proforma. Cutaneous examination with special reference to the morphology, distribution, symmetry of lesions and pattern were mapped on to a chart. Clinical severity was assessed during each visit using the clinical severity score(CSS), on the basis of itching(A), morphology of lesions(B) and the area of body involvement(C).The final score was calculated using the equation

$$CSS = (A+B+C) \times 10 \text{ (maximum score of 100).}$$

Each patient was then subjected to baseline investigations like complete hemogram, blood sugar, liver and renal function tests, urine analysis, chest X ray and at each follow up visit.

Group A (N=12) patients were treated with one tablet of azathioprine (50 mg) as a test dose and asked to for one week. Then they were given oral Azathioprine 300 mg weekly as a single dose of 6 tablets of 50 mg each, half an hour after meals for about 3 months.

Group B (N=10) patients were treated with one tablet of azathioprine 50mg orally once daily for 3 months.

No other immunosuppressive agents or topical corticosteroid were prescribed during the study period other than emollients, barrier creams and anti-histamines. Each patient was followed up at 4, 8 and 12 weeks. At each follow up, improvement in subjective symptoms and cutaneous lesions, compliance and side effects to therapy were assessed. Response to treatment was graded as excellent (>60 %), good (40-60%) and poor (<40%). Serial clinical photographs were taken during every visit. After the end of third month both groups were advised to come for regular follow up at monthly intervals for the period of two months.

At the end of the study, data were subjected to statistical analysis using computer software Microsoft Excel and Statistical Packages of Social-Sciences (SPSS-21). The CSS score in both groups were compared at each visit using Analysis of variance (ANOVA). Independent sample 't' test was performed to assess CSS score between groups. A 'p' value less than 0.05 was considered to be statistically significant. The efficacy was assessed on the basis of a decrease in the mean CSS at 4, 8 and 12 weeks follow up relative to the baseline CSS score.

Table 1 Clinical Severity Score

Score	Itching	Morphology	Area of involvement
0	No itching	No lesions	Face only
1	Mild	Papules	Face, neck and hands
2	Moderate	Plaques	All exposed sites and flexures
3	Severe	Lichenified plaques	Erythroderma

RESULTS

A total of 22 patch test confirmed cases of parthenium dermatitis were enrolled in the study. Out of 22 cases, 12 cases were in group A and 10 cases in group B. The mean age of the study patients was 52.54±6.56 years. Males outnumbered females in our study, as males were 81.82% and females were only 18.18%.Hence male: female ratio was 4.5:1.Most of our patients had a duration of 6-10 years with a mean duration of 6.4±2.32 years. Farmers(52%) constituted maximum number of cases in our study.60% of our cases belongs to rural population followed by suburban group(30%).Exposure to parthenium weed(65%) was found to be the most common predisposing factor. Seasonal exacerbation in summer and winter was noted in 20% and 10% respectively. The commonest clinical pattern encountered were classical airborne as seen in 14 cases (63.64%) followed by photo-exposed in 22.73%. Less common patterns observed were lichenoid eruption and prurigo nodularis in less than 5% of cases.

Response to Treatment

Table 2 CSS score analysis within group

Assessment CSS score each visit	Group A (AZA-W) Mean	Group B (AZA-D) Mean
V1 0 week	44.65 ± 12.22	42.69 ± 11.56
V2 4th week	30.61 ± 9.49	33.87 ± 9.97
V3 8th week	20.28 ± 7.50	27.66 ± 9.14
V4 12th week	13.83 ± 4.84	23.34 ± 8.37
ANOVA	'F' value	'P' value
A	35.592	0.001
B	21.614	0.001

The detailed CSS score analysis compared within group was performed and tabulated in table 2. The mean value of baseline CSS score in group 'A' was 44.65 ± 12.22. It was further reduced to 13.83 ± 4.84 at the 4th visit (12th week). Likewise, the drop in CSS score was gradual from visit 1(42.69 ± 11.56) to 4th visit (23.34 ±8.37) in Group B. The assessment of improvement of disease within group was carried out by ANOVA. The CSS assessment of both groups compared with baseline values showed significant reduction in every visit.

Figure - 1: CSS score analysis within group

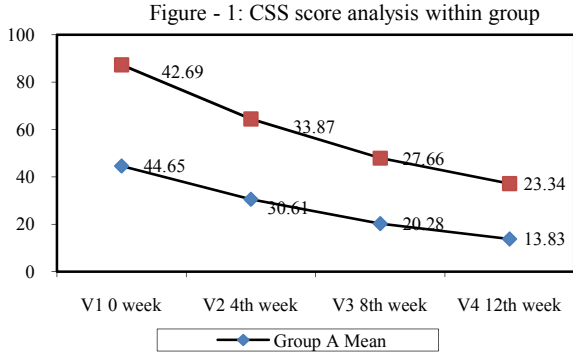


Table 3 CSS score comparison (visit wise) between groups

CSS Score comparison (visit wise)	Mean Group A (AZA-W)	Mean Group B (AZA-D)	't' value	'P' value

1st Vs 2nd difference	14.04 ± 5.37	8.82 ± 5.01	2.356	0.029
2nd Vs 3rd difference	10.32 ± 3.60	6.21 ± 3.69	2.631	0.016
3rd Vs 4th difference	6.85 ± 4.04	4.02 ± 2.19	3.933	0.001
1st Vs 4th difference	30.81 ± 8.62	19.35 ± 4.99	3.889	0.001

Visit wise CSS comparison between groups showed higher clearance rate in group A than group B. The difference of reduction of severity from baseline value was found to be significant during each visit. The overall difference of CSS from baseline score at 4th visit in group A was 30.81 ± 8.62, where it was only 19.35 ± 4.99 in group B.

Figure -2: CSS score comparison (visit wise) between groups

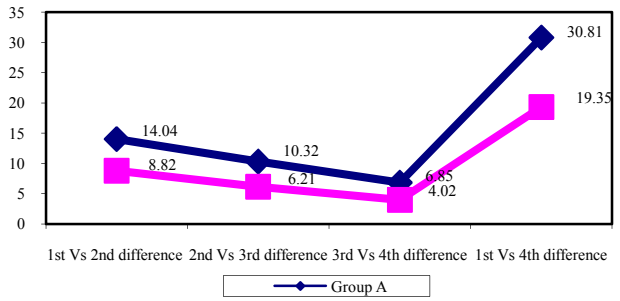
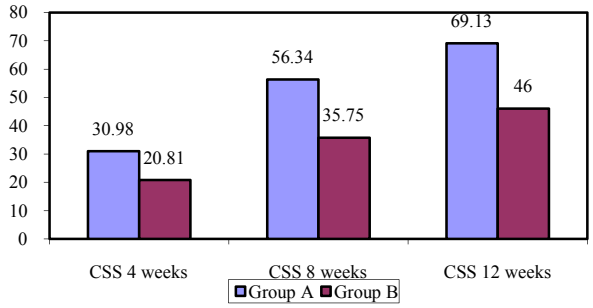


Figure -3: CSS score improvement in percentages



The CSS score improvement in terms of percentages is presented in Figure 3. 12th week improvement is again comparatively higher for group 'A' (69.13) than group B (46%).

Relaspe

Table 4 CSS score comparison (visit wise) during follow up

Visit	Group A (AZA-W) Mean	Group B (AZA-D) Mean	'Z'	'P'
V5 16th week	12.58 ± 3.91	25.39 ±11.40	3.390	0.006
V6 18th week	12.68 ± 5.89	28.34 ±16.13	2.911	0.014

The mean follow up CSS score after completing treatment at 16th and 20th week was comparatively less in group A compare to group B even during follow up visits and further the difference was statistically significant. The overall recurrence rate is 44%. Group 'B' patients relapsed more (50%) when compared to group 'A' (16.67%),

Adverse Effects

Table 5 Side effects in patients of the two groups

Side effect	Group A (AZA-W) (N=12)	Group B (AZA-D) (N=10)
Nausea	2(16.67%)	1(10%)
Vomiting	4(33.33%)	2(20%)
Diarrhoea	2(16.67%)	1(10%)
Fever	1(8.33%)	0
Cutaneous infection	1(8.33%)	0
Headache, myalgia	2(16.67%)	1(10%)
Mixed	2(16.67%)	1(10%)

In our study, most of the patients tolerated the therapy very well. Few patients in group A showed higher incidence of gastrointestinal side effects with nausea and vomiting in about 16.7% and 33.33% respectively. In group B patients, only 10% and20% of cases had nausea and vomiting. Other minor side effects like transient leukopenia and herpes zoster in one patient each (8.3%) in group A.16.67% and 10% in group A and group B had more than one side effects. The side effects were commonly noticed during 3rd month than 1st and 2nd months of therapy.

DISCUSSION

Parthenium dermatitis is a common, chronic, relapsing dermatoses which follows a prolonged course with more frequent exacerbations and remissions and accounts for 40% of cases attending contact dermatitis clinics. Corticosteroids are the mainstay of treatment in parthenium induced dermatitis. However, regular intake of corticosteroids for prolonged periods is often associated with severe and sometimes irreversible systemic side effects.[6]

Azathioprine 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 due to inhibition of the activated T-lymphocytes, the cells primarily responsible for the development of dermatitis. The drug can be used safely in pulse and daily doses even on long-term use, without any significant side effects.

In our study the response to treatment with weekly pulse doses and daily dose was compared. CSS score was improved significantly in both groups following the treatment. The statistical analysis also shows that there was more significant improvement of CSS score in group A (p=0.001) than group B from baseline at 4th, 8th and 12th weeks of treatment.

In group A, the mean CSS at 4, 8 and 12 weeks decreased respectively to values of 30.61±9.49, 20.28±7.50, 13.83±4.84 from the mean value of 44.65±12.22 at 0 week, with statistically significant percentage decline in the mean of 30.98,56.34 and 69.13 respectively. The mean CSS score for group B at baseline was 42.65 ± 12.22 which was reduced to 23.34 ± 8.37 and the magnitude of improvement in group B was only 46%. Such high efficacy of Azathioprine is consistent with other studies.[7,8,9,10]

Patients in group A were observed to have more side effects like nausea (16.67%), vomiting (33.33%) and diarrhea (16.67%) than group B patients. Only 20% of group B cases developed gastrointestinal adverse effect. But none of these side effects were significant enough to warrant stoppage of therapy in any patient. No case of myelotoxicity and liver damage was encountered in our study. However, studies shown that AZA can be safely prescribed and these side effects were only transient, which return to baseline within few months without stoppage of drug.[11]

Though there was excellent response to both regimens of azathioprine, few cases relapsed after stopping the treatment at 12 weeks. The overall recurrence rate is 44%. Relapse rate was found to be higher in group 'B' patients (50%) than group A (16.67%).

Limitations of our study were smaller sample size, duration of treatment and follow up were not standardized and estimation of thiopurine methyl transferase (TPMT) enzyme assay prior to treatment due to resource poor setting.

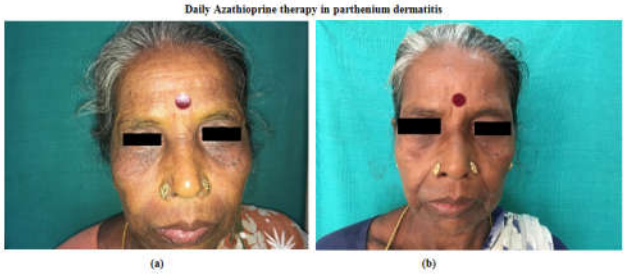


Figure 5 (a) before treatment (b) after treatment

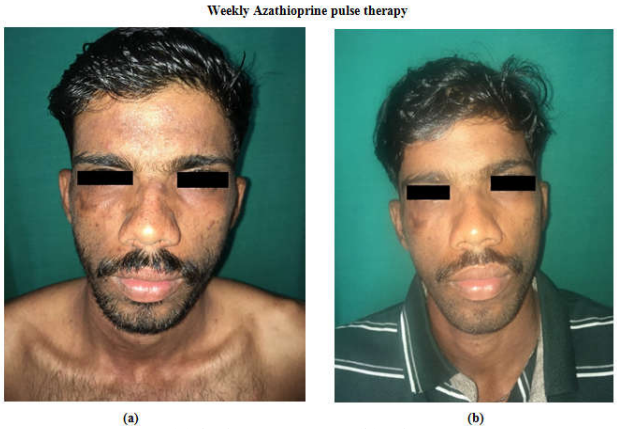


Figure 6 (a) before treatment (b) after treatment

CONCLUSION

Our study concluded that both weekly and daily regimens showed a significant reduction of CSS. However, the statistical comparison proved efficacy of WAP was superior to daily AZA in the treatment of ABCD. Few side effects were encountered in WAP, which can be tackled conservatively without stopping the treatment.

The relapse rate and compliance also emphasize the supreme efficacy of WAP in the management of ABCD. Prior estimation of TPMT can be done, whenever facilities permit. This study also suggests that azathioprine is a safer drug in both pulse and daily doses even for long term use under regular monitoring in whom systemic corticosteroids are contraindicated. Thus, the longer the therapy is given, the better the efficacy, with progressive decrease in severity score. However, further large-scale studies are needed in near future to support our findings.

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