ORIGINAL ARTICLE

EFFECTIVENESS OF FRACTIONAL CARBONDIOXIDE LASER WITH TOPICAL METHOTREXATE VS TOPICAL PUVASOL IN TREATMENT OF VITILIGO

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Background: Vitiligo is an autoimmune disease characterized by patches of depigmentation on the skin. As skin is the major contributor to one's social image and appearance, this disease impairs one's quality of life to a significant extent. Dermatologists are continuously trying to find more and better treatment options, in addition to steroids, calcineurin inhibitors, immunomodulators and phototherapy. The aim of our study was to compare the effectiveness of topical methotrexate in combination with fractional carbon dioxide laser with topical psoralen with solar UVA (PUVASOL). Our hypothesis was that the Carbon dioxide laser-Topical Methotrexate combination is better than topical PUVASOL. **Methods:** It was a double blinded randomized Control Trial carried out in the Dermatology OPD of a tertiary care hospital in Rawalpindi over a period of 05 months, i.e., 05.03.24 to 20.07.24. Thirty-four vitiligo patients fulfilling the inclusion criteria were recruited after informed consent. Sampling was done by non-probability consecutive sampling and the participants were randomly allocated to either of the two groups by block randomization. Seventeen of them were assigned to group A and treated with Fractional CO-2 laser followed by topical methotrexate 12.5 mg/ml application. Weekly sessions were done for 4 months. In Group B, topical PUVASOL was used on alternate days for 04 months for 17 patients. One patient from each group was dropped due to non-compliance issues. An independent observer noted the clinical improvement. Patient satisfaction and complications were also recorded. Data collected was analyzed using IBM SPSS 27.0 (Software Package for Social Science). **Results:** Statistically significant difference in results of Group A as compared to Group B, regarding clinical improvement (p-0.003) and patient satisfaction were noted (p 0.005). There was no significant difference in the side-effect profile of both groups (p=0.627), with 43.75% patients having no side effect at all. **Conclusion:** Combination treatment of fractional CO-2 laser and topical methotrexate is better than topical PUVASOL in managing vitiligo.

Keywords: Fractional Carbon dioxide laser; Topical methotrexate; Topical PUVASOL; Vitiligo

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INTRODUCTION

Dermatologist frequently face the challenge of treating vitiligo, which has a worldwide prevalence of 0.5% to 2%.[1] This dermatosis is characterized by acquired paucity of melanocytes in the effected skin patches due to autoimmunity targeting them. Some studies have shown increased TNF-@ levels in vitiligo patches as compared to perilesional and normal skin, emphasizing its role in the disease pathogenesis.[2] Patients effected with vitiligo experience low self-esteem and have negative functional impact on quality of life as measured by DLQI, especially women, people aged more than 40 years, and people with Fitzpatrick skin types IV and higher.[3–5]

The fractional CO2 laser is a promising adjunctive treatment option to conventional strategies for management of vitiligo. This laser, with its ability to stimulate melanogenesis and enhance drug penetration, has earnedits therapeutic position as a potential add-on treatment modality for refractory lesions. Its ability to stimulate the multiplication of melanocytes and promote the re-pigmentation of affected areas underscores its potential as a therapeutic solution.[6] Some studies show that adding the fractional CO2 laser before topical drugs in vitiligo treatment led to improvement inrefractory lesions and improved the speed of recovery.[7–9] The mechanism of action of Fractional CO2 laser in the management of vitiligo is based on its ability to release inflammatory cytokines from the laser damaged skin.[10] This leads to the

proliferation and migration of melanocytes in the laser treated areas, while facilitating the absorption and enhanced delivery of therapeutic agents through laser induced controlled micro injuries forming temporary microscopic pores within the laser treated skin. Italso triggers collagen, elastin synthesis, and melanocyte migration, aiding re-pigmentation. Based on these effects, Fractional CO2 laser therapy presents a favourable approach for combination therapy in the management of vitiligo.[11]

BAAD (British association of Dermatology) guidelines 2022 have also recommended combination of fractional carbondioxide laser with another topical medication. They have mentioned combining CO2 laser once a month for 5 months in combination with topical 5-fluorouracil applied once a day for 1 weeks every month till 5 months; in adults with nonsegmental vitiligo on the hands and feet if other treatments have been in effective.[12]

Methotrexate is a folate antagonist. It has been used in the management of psoriasis, atopic dermatitis and other autoimmune disorders including vitiligo in dermatology.[13–15] Its mechanism of action in vitiligo as shown by studies include down regulation of T-cells capable of making TNF-@ and upregulation of interleukin -10 producing T-cells by polyclonal activation.[16] It possibly decreases the TNF-@ induced NF-kB activation in the lesional skin.[17] Although systemic administration of methotrexate, i.e., weekly oral or subcutaneous administration is the common treatment modality in dermatology but studies have shown that topical methotrexate 1% gel twice daily for 12 weeks has shown significant improvement of the vitiligo with no side effects reported. So, this proposes that this drug topically can be used for vitiligo therapy. But studies could not ascertain the exact topically effective dose.[14,18]

BAAD guidelines for treatment of vitiligo recommend considering PUVA or PUVAsol in adults with vitiligo if treatment with NB-UVB is unavailable or has been in-effective.[12] PUVASOL stands for psoralen and UVA obtained by solar light as sunlight is a rich source of UVA. A major disadvantage of sunlight as a mode of phototherapy for UVA is the inability to standardize and calculate the exact amount of UVA used during each treatment, hence making it a crude phototherapy modality. The total amount of UVA absorbed by the skin after one exposure varies widely depending on the season, time of the day, latitude, and conditions of the atmosphere. Other disadvantages are lack of privacy and phototoxic blistering in some cases. According to a study conducted by Balasaraswathy *et al*., the best time of the day for PUVASOL is between 0915 hrs-1115 hrs. and 1430–1530 hrs. respectively.[19] There is minimal unwanted exposure to UVB and infrared light at these times. Topical PUVA with 8 Methoxypsoralen (8MOP) may be used in patients with smaller lesions of vitiligo involving less than 5% of body surface area. 0.01–0.1% 8MOP in a cream or lotion base is applied to the affected area and irradiation is done after 30 min. Application of sunscreen to the surrounding uninvolved skin can prevent undue tanning. Trimethoxypsoralen (TMP) and 5MOP are more phototoxic topically. There are different concentrations of topical psoralen mentioned in literature ranging from 0.1– 5% 8 MOP with dilution done with eau-de-cologne or Propylene glycol or white soft paraffin. After 30 min, the patches are exposed to sunlight starting with 0.5–1 min. Preferred and commonly practiced treatment protocol in our dermatology out-patient department involves 2–3 times/week application followed by photo-exposure. Duration of sun exposure should be slowly increased by 0.5–1 min every week till slight erythema appears after which the time is kept constant.[20]

These treatments options mentioned in the literature gave us an idea of combining fractional carbondioxide laser with topical methotrexate instead of 5-flourouracil as mentioned in BAAD guidelines and comparing it with topical PUVASOL treatment. We thought of preferring PUVASOL instead of UVB phototherapy due to feasibility and cost-effectiveness issues, as UVB phototherapy is an office- based procedure which required at least twice weekly visits to OPD. We had the rationale of establishing a new and feasible treatment modality for this auto-immune disease.

The primary objective of this study was to determine the effectiveness of fractionated resurfacing carbon dioxide LASER and topical methotrexate with topical PUVASOL in cases of vitiligo effecting less than 10% body surface area. The secondary objectives included comparing the patient satisfaction and side effect profile in both treatment groups.

MATERIAL AND METHODS

This double blinded randomized control trial (RCT) was registered with Iranian Registry of Clinical Trials: IRCT20230816059168N2 against membership number of 59168. Hospital ethical committee approved the study. it was conducted in the Dermatology outpatient department of a tertiary care hospital in Rawalpindi over a period of 05 months, i.e., 5th March 2024 to 20th July 2024 after registry of the trial. The RCT had two parallel intervention groups. Sample size was calculated by using epi info sample size calculator version 3. Taking 2 –sided significance level of 95% and power 80%, we took sample size of 15 in each group based on comparing mean difference in the treatment response of two interventions in vitiligo.[21]

Inclusion criteria were patients willing to participate in our study, ranging from age group of 10–70 years of both sexes and having vitiligo less than or equal to 10% BSA involvement. Exclusion criteria included patients using or have used other treatments for vitiligo, pregnant women or lactating women (as methotrexate and psoralen are both contraindicated in pregnancy and lactation), patients with segmental vitiligo, patients on immunosuppressant medications due to other diseases, patients having connective tissue diseases, epilepsy or photosensitivity disorders, patient having previous radiotherapy or phototherapy (to avoid erythema recall) , patients with personal or family history of melanoma and non-melanoma skin cancers and patients having history of hypersensitivity to the drugs used in our study.

Total 34 patients presenting to dermatology OPD were recruited in the study after applying the inclusion criteria, following their informed consent and using simple, non-probability consecutive sampling. Later on, patients were randomized into two equal groups, by block randomization method, of which 32 patients in total, completed the clinical trial. Patients were counselled about their respective treatment protocols. Their Fitzpatrick skin types were recorded. Vitiligo was confirmed by Wood's lamp examination. Location of their lesions with body surface area of involvement calculation and VASI (Vitiligo area severity index) was done by an independent observer from dermatology department. Demographic data i.e., age, gender, family history, duration of the disease was recorded along with baseline photograph.

For Group A, topical eutectic mixture of local anaesthetic cream, i.e., prilocaine and lignocaine, was applied over the patient's lesions for 30–45 min. A 10,600-nm fractional carbon dioxide (CO2) laser device was use in a resurfacing mode with pulse energy of 70–100 J/cm^2 and coverage and a spot density of 150 spots/cm^2 in a fortnightly frequency for a total of 08 sessions. Immediately after each session, topical 25 mg/ml methotrexate injection was diluted to 12.5 mg/ml, and not more than 01 ml was massaged on the treated area and a dry dressing was done for 12 hours afterwards.

Group B was advised topical psoralen with the name of Lukodermine by Howards Pharma. The ointment contains Methoxsalen as its active ingredient and comes in a pack size of 30 gm .5% ointment was applied for 45 minutes on the vitiligous patch prior to sunlight exposure. Initially photo exposure was done for 3 minutes and then incrementally increased by 30 seconds every time until a moderate persistent erythema was achieved. This treatment was done thrice a week. Treated area was washed with soap and water and sunscreen was applied with SPF of at least 50 or more and a UVA protection too. Patients were examined monthly for 04 months for assessment of re-pigmentation.

A blinded independent medical observer performed clinical assessments using the following subjective grading scale: 1, <25% minimal re-pigmentation; 2, 26–50% mild re-pigmentation; 3, 51–75% moderate re-pigmentation; 4, >75% excellent re-pigmentation.

Patient satisfaction was also assessed by grading scale, i.e., 1. Unsatisfied, 2. Partially satisfied, 3. Completely satisfied. Total VASI was also calculated at the end of the study period i.e., 04 months after the start of treatment. Side effects were also noted in each group.

One patient from group A dropped from the study as he did not follow up after 2 visits and similarly another patient from group B developed blistering after PUVASOL therapy and was dropped from the study after appropriate management. Data collected was analyzed using IBM SPSS 27.0 (Software Package for Social Science). As most data was categorical and sample size was small, so non-parametric tests were used. We also checked for the normal distribution of data using histogram and it came out to be not normally distributed. Descriptive analysis for demographic data like age, sex, Fitzpatrick skin type, duration of disease, family history and location of lesions was done showing frequency and percentages for categorical and numerical variables. Measures of central tendency, i.e., mean and mode and dispersion (Standard deviation, range, variance) were also done Chi-square test was used to compare the outcomes in the two independent samples. The Body surface area in both groups was a continuous variable and was assessed by Independent-Sample Mann Whitney U test. *p*-value of less than 0.05 was regarded as statistically significant.

RESULTS

Thirty-two patients, i.e., 16 in each group completed the study. Overall, 15 (46.8%) patients were male and 17(53.125%) were female in both groups. Out of these 15 males, 6(40%) were in group A and 09(60%) were in group B. Similarly, 10 (58.8%) females were included in group A and 7 (41.176%) in group B. *p*-value was 0.288 (insignificant as it is <0.05) indicating groups were similar in terms of demographics examined. Other demographics are mentioned in the table below.

Test was carried out to check the normal distribution of our data. As sample size was less than 50 in each group, Shapiro-wilk test was preferred for the pre and post intervention VASI. *p*-value was 0.034 and less than 0.001 for them respectively. Null hypothesis of normality was rejected meaning that the data was significantly non-normal as values were less than 0.05.

As the data was not normally distributed, non-parametric tests, i.e., chi square test and others were used for data analysis.

Table-1: Summary of results-demographics, primary and secondary outcomes of the study

1. Frequencies of Fitzpatrick skin types in Group A and B			
Fitzpatrick Skin Type (Total Frequency and % age)	**Group A (n= 16) (Frequency and %age)**	**Group B(n=16) (Frequency and %age)**	**p-value**
II 1 (3.125%)	1 (3.125%)	0	0.785
III 12 (37.5%)	6(18.75%)	6(18.75%)	
IV 15(46.87%)	7 (21.875%)	8 (25%)	
V 4 (12.5%)	2 (6.25%)	2 (6.25%)	
2. Disease Duration			
< 01 year 14 (43.75%)	8 (25%)	6 (18.75%)	0.544
1-5 years 15 (46.875%)	6 (18.75%)	9 (28.1%)	
>05 years 03(9.37%)	2 (6.25%)	1 (3.125%)	
3. Location of lesions			
1-Face 9 (28.1%)	2(6.25%)	7(21.875%)	0.318
2-Trunk 10(31.25%)	7(21.875%)	3(9.375%)	
3-Upper Limb 2(6.25%)	1 (3.125%)	1 (3.125%)	
4- Lower Limb 8(25%)	4 (12.5%)	4 (12.5%)	
5-Multiple sites 3(9.375%)	2 (6.25%)	1 (3.125%)	
4. Age distribution in Group A and B			
< 30 years 24(75%)	11(34.375%)	13(40.625%)	0.414
30 years or more 8(25%)	5(15.6%)	3(9.375%)	
5. Family History in Group A and B			
Yes 9(28.1%)	5(15.6%)	4(12.5%)	0.694
No 23(71.87%)	11(34.375%)	12(37.5%)	
6. Side Effects in Group A and B			
None 14(43.75%)	8 (25%)	6(18.75%)	0.627
Irritation 09(28.1%)	5 (15.6%)	4 (12.5%)	
Pain 05(15.6%)	2 (6.25%)	3 (9.375%)	
Koebnerization 2(6.25%)	1 (3.125%)	1 (3.125%)	
Other 2(6.25%)	0	2 (6.25%)	
7. Evaluation of improvement by Blinded Dermatologist in Group A and B			
1-<25% (Minimal) 05(15.6%)	0	5 (15.6%)	0.003
2-26-50% (Mild) 13(40.6%)	4 (12.5%)	9 (28.1%)	
3-51-75% (Moderate) 09(28.1%)	8 (25%)	1(3.125%)	
4->75% (Excellent) 05(15.6%)	4 (12.5%)	1 (3.125%)	
8. Patient Satisfaction in Group A and B			
Unsatisfied 6(18.75%)	0	6(18.75%)	0.005
Partially Satisfied 15(46.8%)	7(21.875%)	8(25%)	
Completely Satisfied 11(34.37%)	9(28.5%)	2 (6.25%)	

Table-2: Comparison of Pre and Post treatment VASI in both groups

VASI Pre and Post treatment in Group A				
	Mean±SD	Min	Max	*P*-value
Pre (n=16)	2.95±1.39	0.75	5.25	<0.001
Post(n=16)	1.189±0.906	0	3.5	
VASI Pre and Post treatment in Group B				
Pre(n=16)	3.5±2.368	0.5	8.5	<0.001
Post(n=16)	1.77±1.546	0	6	

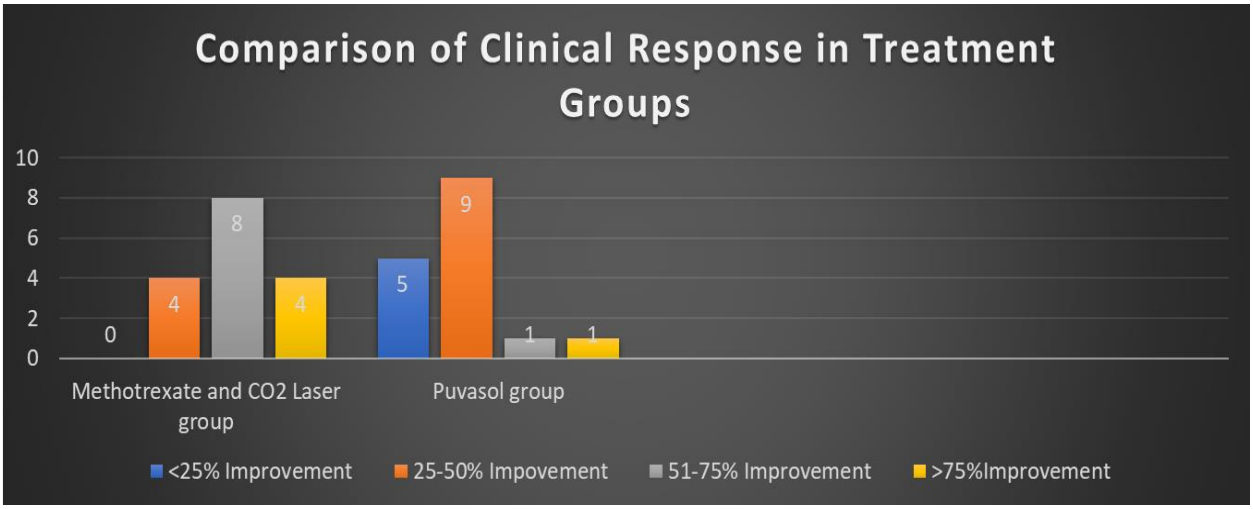

Figure-1: Clinical Response in both treatment Groups

Table-1 shows significant *p*-values for improvement and patient satisfaction in both groups, i.e., 0.003 and 0.005 respectively, indicating significant difference in both the treatment groups. The values are significantly better for group A as compared to group B.

The *p*-value for BSA was 0.28 showing insignificance and supporting the null-hypothesis that the distribution of the variable is the same across both categories. Mean BSA involved was 4.69 with SD of 2.54 with minimum value of 1 and maximum of 9.5. Mean rank in group A was 14.74 and in group B it was 18.28.

Wilcoxon signed Rank test (a non-parametric test) was used to compare the continuous variable, i.e., VASI score before and after treatment in both groups in place of paired t-test. The results are as follows. There was a significant difference pre and post treatment with in both groups showing that both treatments improved vitiligo. But again, based on the comparison of clinical improvement as mentioned before in table-1, effectiveness of treatment used for group A was better than group B (p=0.003).

DISCUSSION

To our knowledge, this is the first randomized controlled trial evaluating the efficacy and safety of fractional carbon dioxide laser usage in combination with topical methotrexate in the treatment of vitiligo in comparison with topical PUVASOL. Here the usage of carbon dioxide laser is done for two purposes; firstly, using it as a treatment modality for vitiligo and secondly using it as drug delivery system for methotrexate.

Fractional carbondioxide laser treatment has been used either alone or in combination with other treatment options like NB-UVB, platelet rich plasma therapy, topical potent steroids, salicylic acid and tacrolimus in cases of vitiligo. A review published in Nov 2023 mentions pain, burning sensation, erythema, swelling, pruritus and hyperpigmentation as minor side-effects of this treatment option with good efficacy.[11] Melanogenesis stimulation as a result of microinjury induced inflammatory cascade following this laser along with enhanced drug delivery through micropores is the proposed mechanism of action of this drug here.[8,11]

Liu *et al* in 2019 did a multi-centeric research study on 289 patients of acral vitiligo combining carbon dioxide laser, topical betamethasone and NB-UVB and comparing it with topical betamethasone and NB-UVB combination. The overall responsiveness of the first group outperformed the second (p=0.005) with 51.6% and 35.8% improvement respectively.[22] Our study has also shown comparable results as 12 (75%) patients in carbon dioxide laser treated group showed >51% clinical improvement after 4 months of treatment as compared to 2 (12.5%) patients in the topical PUVASOL group. The *p*-value comparing the efficacy of these treatment modalities was significant, i.e., 0.003.

In 2015 Mohamed *et al* compared fractional carbon dioxide laser combined with 5-flourouracil comparing it with either of the two modalities alone in 68 cases of acral vitiligo. 49.8% cases achieved grade 4 re-pigmentation and 6.1% grade 3 re-pigmentation in the Laser combination group.[23] Their results were better as compared to our study as we had excellent response (>75% improvement in 25% of cases and moderate response (25–75% improvement) in 75% of our cases treated with combination of carbon dioxide laser with topical methotrexate.

In another study done by Weshahy R *et al* in 2022 good results were seen as in our study when they combined fractional carbondioxide laser with topical 5-flourouracil cream in 30 cases of non-segmental vitiligo. They used VESTA (Vitiligo extent score for target areas) as an objective assessment tool for vitiligo in their study, but we have used VASI score in our study.[24]

Topical methotrexate has been used with varying degree of success in psoriasis, palmoplantar pustulosis, mycosis fungoides and lymphomatoid papulosis.[18,25–29] 1% Methotrexate gel has been used successfully in cases of localized vitiligo utilizing its mechanism of "local immune-editing".[18] Studies have shown that folic acid supplementation is not required when topical application is used.[25] We have also not used this supplement in our study.

In a comparative study in 2022, Rageb A *et al* used intralesional methotrexate injection at 1 cm interval with 0.02ml/site volume with the maximum of 2.5–5 mg in one session, in cases of localized vitiligo and compared it with intralesional triamcinolone injections. This was done weekly for a total of 6 sessions. 13.3% patients had excellent response and 13.3% had good response in methotrexate treatment group which were less than our statistics of 25% excellent response and 75% moderate response in our methotrexate carbon dioxide laser combination treatment group. The difference could be due to our addition of fractional carbon dioxide laser with methotrexate topical. The pre and post intervention results in both groups in the mentioned study showed p<0.001 which are similar to our results from each treatment group, i.e., p<0.001 for each group.[30]

In a double-blinded randomized study comparing Ruxolitinib with control in cases of vitiligo, mean BSA involved at baseline was 22.05%(SD±18.35) compared to 4.69% (SD±2.54) in

our study.[31] But we had only less than 10% BSA involvement as our inclusion criteria.

In the topical Ruxolitinib for vitiligo study, the mean age was 48.3 years (±15.4).(31)In another study comparing topical tacrolimus with micro needling combined with tacrolimus 80% patients were <30 years of age and 20% were> 30 years of age.[32] In comparison to these 02 studies 75% patients were <30 years and 25% patients were> 30 years in our study.

In our study 46.87% patients were male and 53.125% were females, while in topical Ruxolitinib study 46% were male and 64% were females.[31] In the topical tacrolimus with micro needling study in vitiligo, 6.6% were males and 93.3% were females.[32]

Similarly in the study by Rosmarin D *et al*, 64% vitiligo patients belonged to Fitzpatrick skin type II-III, as the study was carried out in USA. In the study done by Kiran *et al* 67% patients had Fitzpatrick skin type III and 33% had skin type IV.(32) These results are comparable to our study as 46.8% had skin type IV and 37.5 % had skin type III in our study. Both these studies were carried out in the two provinces of the same Asian country, hence a little variation in the skin types was observed.

Family history of vitiligo was positive in 28.125% of our cases, while it was positive in 10% cases by the study done by Kiren *et al*.[32]

Disease duration was less than 5 years in 53.3% of cases in the study by Kiren *et al* and 90.6% of our cases.(32) In fact 43.75% of our cases had disease duration of < 1 year.

Comparing the side effect profile, 43.75% cases had none of them, 28.125% had irritation of the treated skin, 15.6 % had transient pain in the treatment site and 6.25 % had Koebnerization of lesions and 6.25 % had other adverse effects like blistering with treatment and scarring. 25% patients with side effects belonged to the group A and 31.25% belonged to group B. Koebnerization was not noted in other studies.[23,25,30] Pruritus and acne were the reported side-effects in the study utilizing topical Ruxolitinib in vitiligo.[31]

CONCLUSION

This study shows that combination of fractional carbon dioxide laser with topical methotrexate is a favorable and a novel treatment option for vitiligo cases involving <10%BSA. Results with topical PUVASOL were also comparable, but patient satisfaction and grading by observer about efficacy, favors the methotrexate and fractional carbon dioxide combination.

Limitations

We did not check the blood levels of Methotrexate after topical application following Laser. Measuring this could tell us better about bio availability of the topically applied drug delivery method. Laboratory testing for side effects of methotrexate like myelosuppression and hepatotoxicity were also not done. Follow up of cases for few months to monitor disease relapse was also not done.

Conflict of interest

Authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

Samina: Conceptualization of study design, literature search, data collection. SS: Data analysis, interpretation, literature search, write-up. NM: Literature search, data collection. BR: Data collection, proof reading. ATUD: Proof reading.

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