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Split Dosage Weekly Regimen of Oral Methotrexate is Associated With Improved Side Effect Profile in Rheumatoid Arthritis Patients: A Quasi-experimental Study.

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RESEARCH ARTICLE

Split Dosage Weekly Regimen of Oral Methotrexate is Associated With Improved Side Effect Profile in Rheumatoid Arthritis Patients: A Quasi-Experimental Study

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Abstract

Background and objectives: **Methotrexate (MTX) is globally used by physicians to treat patients with Rheumatoid Arthritis (RA). Previously conducted researches indicate prevalent side effects associated with conventional once-weekly dosage amongst a population sample of patients consuming MTX. The objectives of our study were to find out whether there is a difference between the two studied regimens in efficacy and adverse effects of methotrexate.**

Materials and methods: **Study participants were recruited from the outpatient rheumatology department after ethical approval and informed patient consent. Disease activity was assessed at baseline with various reliable and validated scales (SDAI, PAS, DAS-28 among others) after the propensity score-matched 1:1 among the two groups. One group continued their once-weekly regimen (group A), while the other group had their dosage of oral MTX split into alternate days per week (group B). The propensity-matched groups of 123 patients each were included in the final analysis.**

Results: **The most frequently reported side effect was decreased appetite, followed by gastritis, nausea, headache, and vomiting. Within the two groups, no significant differences were found in disease activity scales. The only considerable difference was mean corpuscular volume (MCV) being higher in Group A ($p = 0.0128$). Comparison of side effect profile at 6 months after intervention showed improved gastritis (63.4 vs 41.5%), nausea (51.2% vs 35.8%), appetite (74.0% vs 60.2%) and hepatotoxicity (14.6% vs 5.7%) in Group B.**

Conclusion: **An alternate-day regimen may prove more beneficial to the patient's compliance due to fewer side effects and similar efficacy to the conventional dosage.**

Keywords: Joint, Arthritis, Rheumatoid, Methotrexate, Regimen

1. Introduction

Methotrexate (MTX) is a disease-modifying anti-rheumatoid drug (DMARD). It is globally used by physicians to treat patients with Rheumatoid Arthritis (RA) apart from its other uses in many diseases as an immunosuppressant and chemotherapeutic agent. MTX is engrossed by the cells of the human body and is transformed into its active metabolite i.e. polyglutamate, whose half-life is of 3 days.[1] Its anti-inflammatory effect is due to in-vivo formation of the drug's active form which is

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responsible for inhibition of Dihydrofolate reductase and 5-Aminoimidazole 4-carboxamide ribotide. The latency period of MTX is 4–8 weeks.[1,2] MTX decreases pain and swelling, decelerates joint damage, and reduces disease activity over time.[2] It can be given in combination with other drugs including sulfasalazine, hydroxychloroquine, tumor necrosis factor (TNF) Inhibitors, and biological agents such as Abatacept, Tocilizumab, etc.[2]

Commonly prescribed regimen of MTX is a single oral dose per week but the half-life of its active compound is 3 days. Once weekly regimen which is used at present was also validated for the treatment of Psoriatic arthritis.[1] Dosage should be given for at least 6 months in order to accurately evaluate treatment efficacy.[2] 28% higher bioavailability is observed with splitting dosage as compared to a single oral dose, resulting in superior drug efficacy.[3] Splitting the oral dose is a better option than using the parenteral route when a substantial dose of MTX is required to control disease activity.[3] The conventional dosage is started with a dose of 7.5 mg/week, rising every 4–8 weeks up to 25–30 mg/week, respectively. When MTX dose exceeds 15 mg/week, oral absorption decreases by 30%, it is then delivered via the parenteral route.[3] About 95% of patients receive MTX orally with a maximum dosage of 15 mg/week.[2]

Both intramuscular and subcutaneous routes are suitable for MTX administration. Comparatively, subcutaneous administration is more suitable as it causes considerably less pain.[4] The administration of injectable dose increases treatment cost along with the fact that most patients complain of pain at the injection site.[3] Chronic use of MTX results in the occurrence of numerous adverse effects. Methotrexate Intolerance Severity Score (MISS) is higher with parenteral MTX (20.8%) in comparison to oral MTX use (6.2%). Similarly, patients on parenteral dosage have more behavioral symptoms (95%) compared to the ones on the oral route (58.3%). Skipping of dosage and non-compliance to MTX has been a factor reported previously in our population as well as in international studies due to its adverse events profile.[5,6]

Rheumatoid Factor (RF) and anti-citrullinated protein antibodies (Anti-CCP) are associated with Rheumatoid Arthritis.[7] It also involves extra-articular organs including skin, eyes, lungs, heart, kidneys, brain, spinal cord, and intestines. The presence of radiographic joint damage is suggestive of a poor prognosis.[2,8,9] European League Against Rheumatism (EULAR) proposed that patients taking MTX should be given folic acid. It reduces the chances of non-compliance and treatment withdrawal by reducing side effects.[2,10,11]

2. Objectives

The objectives of our study were to find out whether there is an improvement in side effects by splitting the dosage into two halves on alternate days without affecting the efficacy of the drug with optimum disease control. A follow-up period of six months was observed between the changes in dose and response measurement.

3. Materials & methods

This study was conducted at the Rheumatology outpatient department of a tertiary care hospital after ethical approval was granted by the institutional review board. The study protocol complied with the Declaration of Helsinki. The study included patients suffering from RA diagnosed by American College of Rheumatology (ACR) criteria, who were already on MTX. A sample size of 120 was calculated by World Health Organization (WHO) sample size calculator using the formula ($n = z^2\ 1\text{-}\alpha/2\sigma^2/d^2$), by estimating the population means through continuous response variables. The Simplified Disease Severity Index (SDAI) score utilized by a previous study was taken as 20.5 ± 9.2 reported in their patients.[3] Absolute precision required was set at 0.165, confidence interval of 95% and error of margin of 5% gave power of the study as 80.4%. The sampling was done as non-probability consecutive methods. The patients included had active synovitis and were already on oral MTX therapy for at least 3 months before inclusion in the study, along with low-dose steroids (<10 mg/day) and non-steroidal anti-inflammatory drugs (NSAIDs) if indicated by their primary physician. Most of the patients were on hydroxychloroquine as the second DMARD to control disease activity as indicated by the primary physician. The excluded patients were those who were pregnant or had any hepatic or renal derangements or were non-compliant with medication. Patients who previously used other DMARDs including leflunomide or biological agents were excluded from the study. A total of 399 patients were initially screened from the inclusion criteria after excluding the above-mentioned and were obtained informed consent to participate in the study. After consent, the patients were initially screened for skipping of dosage (defined as non-compliance or irregular dosing lasting for more than 2 weeks during any time of drug administration for any period) during their previous MTX dosage. All

participants were checked for complete blood count, liver function enzymes, and renal function tests at baseline. The disease activity was assessed at baseline with various reliable and validated scales. The participants were classified into two groups based on their dosage of oral MTX once weekly or being split into alternate days per week (half dose on Sunday and half on Tuesday) along with folic acid administration on alternate days of MTX administration. Propensity Score for both groups was matched for similarity of baseline characteristics adjusted for covariates including age, gender, duration of RA diagnosis, frequency of dosage at baseline, duration of MTX use, history of skipped dosage, RA factor and Anti-CCP positivity, and other comorbid conditions like diabetes and hypertension, and baseline disease severity scores. The final selection criteria are shown in Fig. 1, with 38 patients excluded from the analysis. The dropout and other exclusions included 15 more individuals. Hence, a total of 246 participants completed the study, 123 being in each group. The patients were followed-up every month in the rheumatology clinic and the outcomes were reported after six months of intervention.

3.1. Statistical methods

All statistical analysis was conducted by Statistical Package for Social Sciences (SPSS version 25.0) for Windows (IBM Corp., Armonk, NY). Data were presented as means and standard deviation, or frequency and percentage. The means and frequencies reported were compared with the student's t-test, chi-square, or Fisher's Exact test as indicated when the expected values in any of the cells of a contingency table are below 5. The normality of data distribution was determined by Shapiro−Wilk test. A p-value of >0.05 was considered to label the data as normally distributed. While, p-value <0.05 indicates non-normal distribution. The scales used to assess the disease activity of RA are listed as follows:

3.2. Simplified disease activity index (SDAI)

This index utilized in our study determines disease activity in patients with rheumatoid arthritis with numerical results of five parameters including tender and swollen joint count (28 joint assessment), patient and physician global assessment of disease activity, and levels of CRP. SDAI index is categorized into four ranges with (< than or equal to 3.3) indicating remission, (>3.3−11.0) indicating low disease activity (>11.0−26.0) indicating moderately debilitating disease while (>26) indicating high activity, respectively. This index was pioneered by Dr. Josef Smolen, consultant rheumatologist at the University of Vienna and Lainz Hospital, Vienna, Austria. It is approved by both EULAR and ACR along with WHO.[12]

3.3. Patient global assessment of disease activity

This scale is also utilized to determine the progress of disease activity, as a component of patient activity scale II, by asking a single question from patients about how well they are performing in their daily life activities (given all the manners in which the disease affects them). This scale ranges from 0 denoting very well to 10 denoting poor status. This scale was pioneered by Dr. Frederick Wolfe, a rheumatologist, and professor of medicine at Kansas School of Medicine.[13]

3.4. Physician global assessment

This criterion of assessment is utilized to determine the severity of disease by monitoring daily reports on the number of joints swollen and tender, acute phase reactants like erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), today's function index, pain score, and patient global score. All recent findings are compared with baseline findings and deviations are recorded in numerical percentage form. All these findings play a vital role in calculating SDAI scores.[14]

3.5. Pain visual analogue scale

This scale is also a component of patient activity scale II, it is utilized to determine the severity of the pain suffered by individuals suffering from RA. This scale also helps in determining activity of the disease ranging from 0 being no pain and 10 being the worst pain one could imagine. This scale also works on patients' quoted grading of pain. It was also envisaged by Dr. Frederick Wolfe.[13]

3.6. Patient activity scale II (PAS-II)

This scale is opted to decipher activity of the disease comprising of two scales (pain visual analogue scale and patient global assessment of disease activity) including a short questionnaire called health assessment questionnaire disability index II (HAQ II). The questionnaire consists of four options (without any difficulty, with some difficulty, with much difficulty and inability) as answers to questions regarding daily life activities. The formula to utilize this parameter of assessment is [PAS= (A X

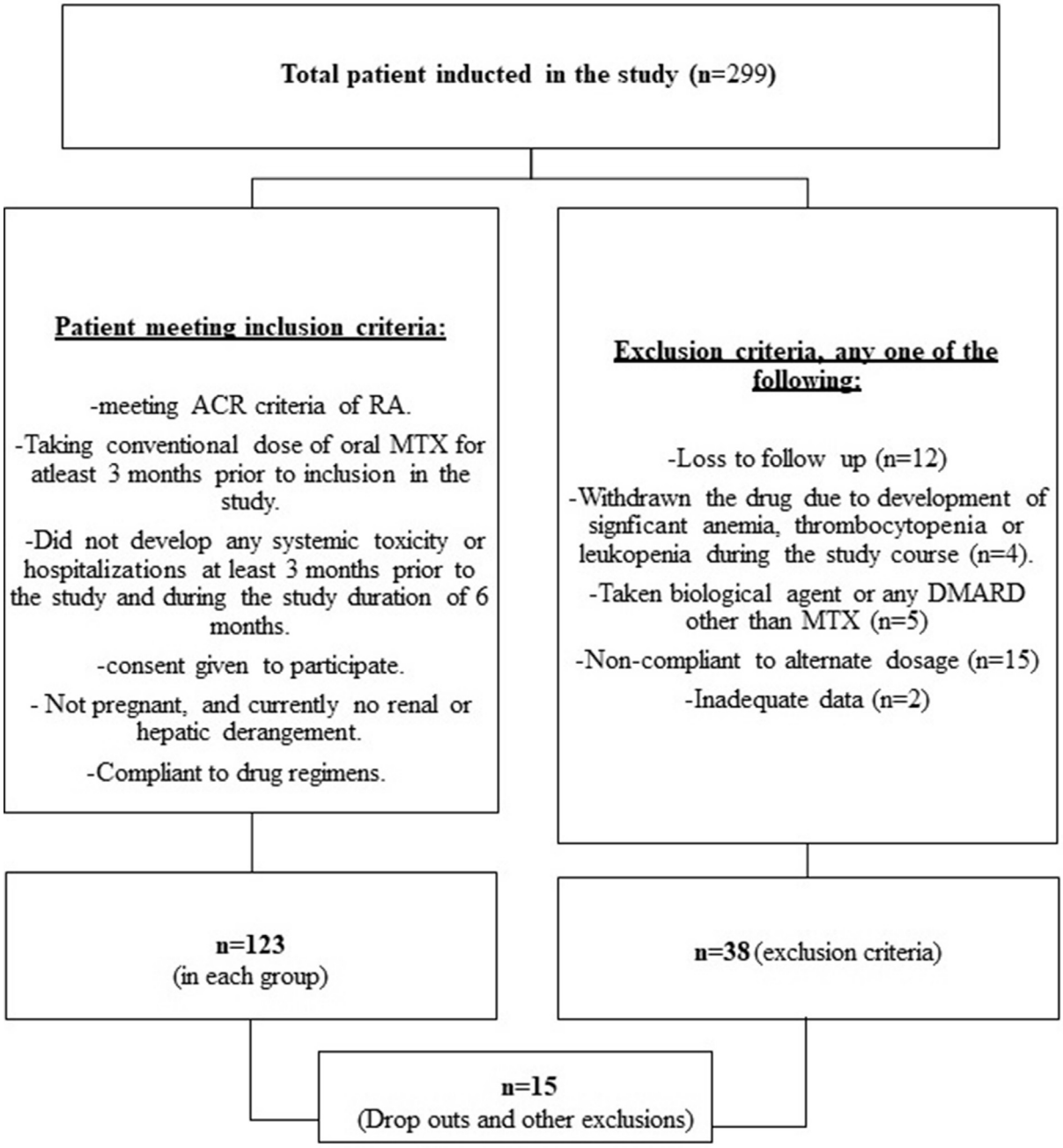

Fig. 1. Methodology (inclusion/exclusion) criteria of the study participants.

3.33 + B+C)/3] with A being (HAQ II), B being pain visual analogue scale and C being patient's global assessment of disease activity. This scale was also created by Dr. Frederick Wolfe.[13]

3.7. Patient activity scale I (PAS-I)

This scale is slightly different than patient activity scale II with an increased number of questions in the questionnaire called health assessment questionnaire disability index I (HAQ I) as compared to HAQ II. Similarly, two scales are utilized (pain visual analogue and patient's global assessment of disease activity). The questionnaire consists of a variety of questions divided into sets of answers like (without any difficulty, with some difficulty, with much difficulty and inability), and two sets of yes and no. These questions are regarding daily life activities, usage of assisted devices, and seeking help from others to perform chores. The formula is similar to PAS II (A X

3.33 + B+C) with A being HAQ I, B being pain visual analogue and C being patient's global assessment of disease activity, respectively.[13]

3.8. Disease activity score (DAS) 28-CRP

This scale determines the severity of rheumatoid arthritis by utilizing numbers of tender and swollen joints, levels of CRP of recent intervals compared with baseline values in percentages, and global health scale denoting quality of life at recent intervals marked on visual analogue scale with 0 being very poor while 10 being very well. DAS-28 CRP is categorized into 4 ranges with a score of <2.6 rendering remission, 2.6–3.2 denoting low activity, 3.2–5.1 denotes moderate activity while >5.1 denotes high activity, respectively. Formula of DAS-28 CRP is [0.56*$\sqrt{}$(Tender Joint Count) +0.28*$\sqrt{}$(Swollen Joint Count) +0.7*ln(CRP)+0.014*(global health)]. This scale was pioneered by Dr. Jaap Fransen, a senior researcher in rheumatology and professor of clinical research at Radboud University, Netherlands.[15]

3.9. Disease activity score (DAS) 28-ESR

This scale determines the severity of rheumatoid arthritis by utilizing numbers of tender and swollen joints, levels of ESR of recent intervals compared with baseline values in percentages, and global health scale denoting quality of life at recent intervals marked on visual analogue scale with 0 being very poor while 10 being very well. DAS-28 ESR is categorized similarly into 4 ranges as with DAS-28 CRP. The formula of DAS-28 ESR is [0.56*$\sqrt{}$(Tender Joint Count) +0.28*$\sqrt{}$(Swollen Joint Count)+0.7*ln(ESR)+0.014*(global health)]. This scale was also pioneered by Dr. Jaap Fransen.[15]

3.10. ACR 20 criterion

This criterion is used to assess the improvement in the number of tender and swollen joints and improvement in three out of five constituents 1) acute phase reactants, 2) patient global assessment, 3) physician assessment, 4) pain visual analogue scale, and 5) disability and functional scale. ACR 20 is suggestive of 20% improvement in the number of tender and swollen joints and 20% improvement in any three out of 5 constituents mentioned above. This criterion is used to determine treatment efficacy in mitigating manifestations of rheumatoid arthritis. ACR 20 criteria was discovered by Dr. Daniel Aletaha, consultant physician of rheumatology in Medical University of Vienna, Austria.

3.11. ACR 50 criterion

This criterion is used to assess the improvement in the number of tender and swollen joints and improvement in three out of five constituents 1) acute phase reactants, 2) patient global assessment, 3) physician assessment, 4) pain visual analogue scale, and 5) disability and functional scale. ACR 50 is suggestive of 50% improvement in numbers of tender and swollen joints and 50% improvement in any three out of 5 constituents mentioned above. This criterion is used to determine treatment efficacy in mitigating manifestations of rheumatoid arthritis. ACR 50 criteria was also discovered by Dr. Daniel Aletaha.

4. Results

The mean age of patients included in the groups was 46.69 ± 15.25 and 48.31 ± 13.37 years respectively, comprising 78.9% females in group A and 76.4% females in group B as shown in Table 1. Out of the total study population of 246 individuals, 67 were diabetic and 79 were hypertensive. While another 39 participants reported a history of skipped dosages of MTX due to side effects, however, statistically insignificant among the study groups.

Frequency of side effects reported by each group is presented in Fig. 2. The most frequently reported side effect was decreased appetite, followed by gastritis, nausea, headache, and vomiting. After splitting the dosage into two halves which were administered to all the patients on alternate days per week for six months in group B, a comparison was done with group A (conventional once-weekly dosage) amongst the baseline biochemical profile and disease activity scales. Mean corpuscular volume (MCV) was found to decrease in group B ($p = 0.0128$) after 6th month of therapy while rest of the laboratory investigations were statistically indifferent in both groups. Among the disease severity scales, Within the two groups, pain analogue scale, patient activity scales, and number of tender joints were indifferent in alternate-day regimen compared to conventional dosage. Also, no significant differences were found in the number of swollen joints, physician and patient's global assessment scores, SDAI, DAS-28 ESR, and CRP scales as shown in Table 2.

Comparison of side effect profile at 6 months after intervention showed improved gastritis (63.4 vs 41.5%), nausea (51.2% vs 35.8%), appetite (74.0% vs 60.2%) and hepatotoxicity (14.6% vs 5.7%) in group B. However, the incidence of gingival bleeding increased with alternate-day dosage of MTX (10.5%

Table 1. Baseline characteristics of study participants (n = 246).

Variables		Frequency/Descriptives		MD/df	p-values
		Group A (n = 123)	Group B (n = 123)		
Mean age		46.69 ± 15.25	48.31 ± 13.37	−1.620	0.377[a]
Gender	Males	n = 26 (21.1%)	n = 29 (23.6%)	1	0.646[b]
	Females	n = 97 (78.9%)	n = 94 (76.4%)		
Mean duration of diagnosis (in years)		7.11 ± 5.25	6.29 ± 5.61	+0.820	0.238[a]
Diabetes		38 (30.9%)	29 (23.5%)	1	0.197[b]
Hypertension		35 (28.4%)	44 (35.7%)	1	0.219[b]
History of skipping dosage		24 (19.5%)	15 (12.2%)	1	0.116[b]

MD: mean difference; df: degrees of freedom.
[a] Indicates student t-test.
[b] Indicated chi-square test.

vs 22.0%) as shown in Table 3. In intention to treat analysis, ACR 20 was achieved in 35% of individuals in group A and 28% of individuals in group B, while ACR 50 in 15% and 18% of groups respectively (statistically indifferent).

5. Discussion

Once weekly regimen of MTX currently used globally is optimum for the treatment of Rheumatoid Arthritis until a large scale, long term and imperishable study is done to assess an alternative dosage scheme.[1] MTX's active compound i.e. polyglutamate has a half-life of 3 days, hence with the usage of the conventional one dose per week regimen drug levels in the body would become suboptimal resulting in poor efficacy. However, previously regulated investigations revealed that regardless of the dosage regimen MTX remains in the tissues for a long duration.[1] Another study compared the once-weekly regimen with a split dosage of 22.5 mg/week MTX. Astonishingly, results in both groups with regards to treatment efficacy and adverse effects incidence were similar.[2] In our study findings, alternate-day regimen showed equal clinical efficacy compared with conventional dosage accompanied by a significantly tolerable side effect profile.

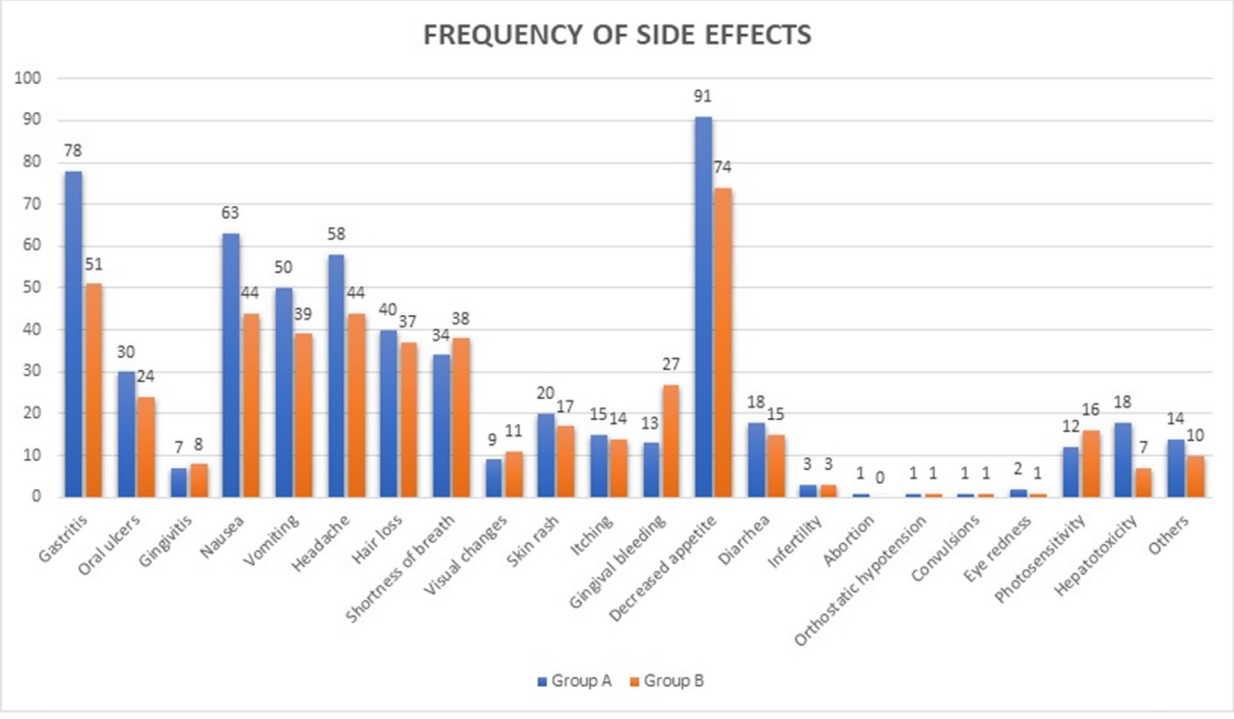

Fig. 2. Comparative frequency of side effects among study groups.

Table 2. Comparison of disease activity and laboratory parameters among the study groups after 6 months.

Parameters	Group A	Group B	df	MD	p-value
Hemoglobin	11.90 ± 1.86	12.24 ± 2.18	238.09	−0.340	0.189
Total leukocyte count	10.24 ± 4.03	9.71 ± 3.69	242.12	0.530	0.283
Platelet count	325.02 ± 107.39	299.46 ± 136.86	230.93	25.560	0.104
Mean corpuscular volume	85.07 ± 9.80	82.11 ± 8.69	240.55	2.960	**0.012***
Serum urea	21.69 ± 7.73	23.36 ± 10.55	223.68	−1.670	0.158
Creatinine	0.70 ± 0.75	0.73 ± 0.98	228.40	−0.030	0.787
ALT	43.14 ± 13.73	37.75 ± 10.52	228.53	5.390	**0.001***
CRP	7.67 ± 8.56	8.00 ± 8.39	243.90	−0.330	0.760
ESR	46.10 ± 24.48	47.88 ± 26.06	243.05	−1.780	0.581
Number of tender joints	8.60 ± 5.52	7.95 ± 4.21	228.04	0.650	0.300
Number of swollen joints	2.76 ± 3.05	2.54 ± 2.84	242.76	0.220	0.558
Patient's global assessment	5.75 ± 2.56	5.59 ± 2.40	242.99	0.160	0.613
Physician's global assessment	5.26 ± 1.90	5.16 ± 1.98	243.58	0.100	0.686
Pain analogue scale	7.46 ± 2.42	6.93 ± 2.44	243.98	0.530	0.088
Patient activity scale 1	6.71 ± 2.52	6.46 ± 2.54	243.98	0.250	0.439
Patient activity scale 2	6.65 ± 2.47	6.54 ± 2.46	243.99	0.110	0.726
SDAI	27.62 ± 11.45	28.08 ± 10.42	241.86	−0.460	0.742
DAS 28 (ESR)	5.31 ± 1.13	5.48 ± 1.18	243.54	−0.170	0.249
DAS 28 (CRP)	4.33 ± 1.05	4.25 ± 0.98	242.84	0.080	0.537

All p-values calculated by student's t-test (* indicates significance of less than 0.05).
SDAI: Simple Disease Activity Index; ALT: Alanine transaminase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; df: degrees of freedom; MD: mean difference.

Previously conducted researches indicate that amongst a population sample of patients consuming MTX, gastric upset was present in (3.6−56.5%), followed by nausea (14.3−32%), stomach ache (11.3−19.7%), vomiting (6.5−14.3%), hepatotoxicity (8.6%), microbial infections (6.8%), anemia (5.7%), joint pain (4.8%), elevated liver enzymes (4.3%), thrombocytopenia (2.1%), stomatitis (2.0−2.1%), pneumonitis (2.2%), pulmonary Tuberculosis (2.2%), leucopenia (1.4−2.2%), nephrotoxicity (2.1%), pancytopenia (1.4%), hair loss (0.5−1.4%), breathing problems (1.4%), visual problems (1.4%), headache (0.7%) and skin rashes in (0.2%) of patients, respectively.[4,11,17−20] Other adverse reactions include gingivitis, anorexia, diarrhea, hematemesis, melena, enteritis, pancreatitis, lymphadenopathy, pericardial effusion, hypotension, increased risk of thromboembolic events, aphasia, hemiparesis, convulsion, stress fractures, conjunctivitis, pulmonary fibrosis, pruritus, photosensitivity, erythema multiforme, dermatitis, renal dysfunction, azotemia, cystitis, hematuria, oliguria, vaginal discharge, gynecomastia, infertility, abortion, fetal defects, vasculitis, impotence, diabetes, osteoporosis, osteonecrosis of bone, tumor lysis syndrome, anaphylactic reactions, transaminitis, interstitial lung disease, oral ulcers, and opportunistic infections.

Table 3. Comparison of side effects among the study groups after intervention.

Sign/symptoms	Group A	Group B	p-value
Gastric upset/gastritis	78 (63.4%)	51 (41.5%)	**0.001**[a]
Oral ulcers	30 (24.4%)	24 (19.5%)	0.461[a]
Gingivitis	7 (5.7%)	8 (6.5%)	0.774[a]
Nausea	63 (51.2%)	44 (35.8%)	**0.018**[a]
Vomiting	50 (40.7%)	39 (31.7%)	0.148[a]
Headache	58 (47.1%)	44 (35.8%)	0.087[a]
Hair loss	40 (32.5%)	37 (30.1%)	0.788[a]
Shortness of breath	34 (27.6%)	38 (30.9%)	0.724[a]
Visual changes	9 (7.3%)	11 (8.9%)	0.804[a]
Skin rash	20 (16.3%)	17 (13.8%)	0.743[a]
Itching	15 (12.2%)	14 (11.4)	1.000[a]
Gingival bleeding	13 (10.5%)	27 (22.0%)	**0.038**[a]
Decreased appetite	91 (74.0%)	74 (60.2%)	**0.036**[a]
Diarrhea	18 (14.6%)	15 (12.2%)	0.720[a]
Infertility	3 (2.4%)	3 (2.4%)	1.000[b]
Abortion	1 (0.8%)	0 (0.0%)	1.000[b]
Orthostatic hypotension	1 (0.8%)	1 (0.8%)	1.000[b]
Convulsions	1 (0.8%)	1 (0.8%)	1.000[b]
Eye redness	2 (1.6%)	1 (0.8%)	1.000[b]
Photosensitivity	12 (9.7%)	16 (13.0%)	0.125[a]
Hepatotoxicity	18 (14.6%)	7 (5.7%)	**0.001**[a]
Others	14 (11.4%)	10 (8.1%)	0.125[a]

[a] Indicates Chi-square test.
[b] Indicates Fisher's exact test.

Dhaon P, et al. and Luis M, et al. in their respective researches assessed disease activity by SDAI score in the range of 0−86.[3,9] While Luis M, et al. reported every other week regimen was associated with less hepatotoxicity but disease activity showed remission equally with once-weekly dosage.[9] We reported an improved side effect profile including liver enzymes. Dhaon P, et al. rendered oral split dosage more effective than once-weekly regimen by improving SDAI but adverse effects were not different in both the groups. Moreover, 13% of patients discontinued the treatment due to adverse

events.[3] In the current study, SDAI was not different in both the groups however, pain visual analogue scale and patient activity scale showed improvement. Pandya S, et al. also reported a decreased number of tender joints with split weekly dosage, similar to our findings.[1] On patients with long-term treatment schedules, shifting dosage from oral to subcutaneous (SC) or starting the regimen with SC route is more potent and likely to improve treatment efficacy.[7] If treatment outcome is not adequate then combination therapy with MTX is recommended.[7] One study proposed that a split dosage of oral as well as parenteral MTX is more potent and effective than a single dose.[9] Drug bioavailability significantly improves when patients use the split dosage modality of MTX rather than a single oral dose.[3]

In patients suffering from psoriasis, hepatotoxicity is noted with increased administration of MTX.[1] Also, no tangible difference is reported in alanine transaminase and aspartate transaminase levels for patients who are on weekly versus every other week MTX dosage.[1] Parenteral delivery of MTX is avowed for reducing gastrointestinal (GI) adverse events but it is usually known for creating greater overall side effects compared to the oral route.[2] In one study it was revealed that 13 patients out of 20 were changed from oral to parenteral route administration due to increased GI adverse effects.[2] Dhaon, et al. suggested that GI side effects came out to be similar with once-weekly oral vs subcutaneous MTX regimen.[3] Patients who are already on once-weekly dosage can be easily shifted to every other week dosing regimen without experiencing a flicker in their disease activity.[11] Another study reported adverse events rate of 58%. Amongst whom 60% of patients were on standard dosage (15 mg/week), while 56% of the patients were consuming larger doses of (25 mg/week), respectively.[16] MTX administration for 3 days in a row can result in sepsis and ultimately death.[8]

There were certain limitations of the current study including observed and unobserved confounders, lack of randomization, and internal validity. The efficacy of an alternate regimen cannot be predicted with this study design, it confers a randomized control trial to compare efficacy. The major limitation included there was no actual controlling for dosage of MTX in our study among the study groups. However, the beneficial observations of improved side effect profiles have been reported successfully.

6. Conclusions

The side effect profile of MTX may be one of the reasons for the patient's non-compliance with the therapy. An alternate-day regimen may be more beneficial for the patient's compliance due to fewer side effects and similar efficacy to the conventional dosage reported in the current study. This approach can be associated with less GI involvement by the drug, more compliance with the regimen, and a tolerable dosage leading to favorable efficacy towards their current disease activity.

Ethical statement

Ethical considerations were fulfilled before the commencement of the study.

Data availability

Data can be made available upon reasonable request from the corresponding author.

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Conflict of interest

The authors declare that they have no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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