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Efficacy of Folinic Acid in Comparison to Folic Acid for Reducing Side Effects of Methotrexate in Children with Juvenile Idiopathic Arthritis

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Abstract

Background: Methotrexate (MTX) is the most effective and commonly used disease-modifying anti-rheumatic drug in the management of juvenile idiopathic arthritis. Several patients develop side effects, which may lead to low quality of life and non-compliance to MTX. To reduce MTX-induced side effects, folic acid supplementation is prescribed by most rheumatologists. Even after that, some patients have symptoms while receiving MTX. **Objectives:** To assess the efficacy of folinic acid in comparison to folic acid for reducing the side effects of MTX in JIA patients. **Material and methods:** In this prospective observational study, newly diagnosed cases of JIA who would be getting MTX were included by purposive sampling. Data were collected using a predesigned questionnaire. Among 40 patients, 20 received folinic acid (Group A), and 20 received folic acid (Group B). Disease activity levels were assessed by JADAS-27 (Juvenile Arthritis Disease Activity Score). Contents from the MISS (MTX Intolerance severity score) questionnaire were used to assess the side effects. All patients were evaluated at baseline, 6th, and 12th weeks. **Results:** There were significant differences in the frequency of MTX-related adverse events between folinic acid (Group A) and folic acid (Group B). Group A patients only had nausea (10% and 15% in the 6th & 12th week respectively) and vomiting (5% at both follow-ups). On the other hand, in addition to nausea (70% and 95% in the 6th & 12th week) and vomiting (20% and 90% in the 6th & 12th week), folic acid group patients had restlessness, crying, and irritability. Self-discontinuation of MTX was present in the folic acid group (5% & 10% in the 6th & 12th week). Improvement of disease activity was more

in the folinic acid group. **Conclusion:** The folinic acid group had significantly fewer side effects. Improvement of disease activity was more and compliance was also better among them. Methotrexate (MTX) is the most effective and commonly used disease-modifying anti-rheumatic drug in the management of juvenile idiopathic arthritis. A number of patients develop side effects, which may lead to low quality of life and non-compliance to MTX. To reduce MTX induced side effects, folic acid supplementation is prescribed by most rheumatologists. Even after that, some patients have symptoms while receiving MTX.

Keywords

Folinic Acid, Folic Acid, Adverse Events, Disease Activity

1. Introduction

JIA is the most common chronic rheumatic disease of childhood and a leading cause of short- and long-term disability. The etiology and pathogenesis of JIA still remain unclear but seem to include both genetic and environmental components. Different factors like immunological abnormalities, cytokine production, infection triggers probably play role in the pathogenesis of the disease. T lymphocytes have a central role in releasing pro-inflammatory cytokines which induces inflammatory synovitis in JIA [1]. The goals of treatment of JIA are to eliminate active disease, normalize joint function, preserve normal growth, prevent long-term joint damage, and disability [2]. Remarkable advances in the treatment of JIA have been made with the advent of new disease-modifying anti-rheumatic drugs (DMARDs). The majority of patients (70% - 80%) with JIA benefit significantly from methotrexate (MTX) therapy [2]. Maximum therapeutic effect usually becomes apparent 4 to 6 months after the beginning of treatment [3]. One study in Bangladesh conducted by Islam *et al.* showed that 92.5% of JIA cases had improvement according to ACR-30 criteria after 6 months of MTX therapy [4].

MTX is an anti-metabolite and a folate analog that competitively inhibits the cellular enzyme, dihydrofolate reductase, which is involved in the essential step of reducing folate to its biologically active form. This results in a depletion of the intracellular stores of "activated" folate and subsequent disruption of cellular metabolism [5]. Gastrointestinal symptoms and an asymptomatic elevation in hepatic transaminase levels are the most commonly observed side effects of MTX [6].

Folic acid (also known as vitamin B9) is a key factor in the synthesis of nucleic acid (DNA and RNA) and performs many biological functions including cell division, growth and erythropoiesis [7]. Folinic acid (5-formyl tetrahydrofolate) is a synthetic form of folate and is designed to bypass the metabolic block. It is readily converted to reduced folic acid derivatives and it does not require the action of dihydrofolate reductase enzyme for its conversion. Its function as a vita-

min is unaffected by inhibition of this enzyme by drugs such as methotrexate [8]. It is currently used as the antidote for severe methotrexate toxicity and prophylactically to reduce the incidence and severity of adverse reactions when intravenous infusions of large doses of methotrexate (0.5 - 10 gram) are employed to treat certain cancers [5].

Despite folic acid use, many JIA patients experience gastrointestinal adverse effects, even before MTX intake, while thinking of MTX. Behavioral symptoms including restlessness and crying, during MTX intake may also be present [9] [10]. It has been reported that folinic acid supplementation may be used to reduce the persistent side effects of MTX, which may occur even after folic acid supplement [11]. The present study was carried out with the aim to assess the efficacy of folinic acid supplementation after MTX therapy in comparison to folic acid, in reducing the side effects without affecting its efficacy JIA patients.

2. Materials and Methods

It was a prospective observational study carried out over a period of 21 months from April 2020 to December 2021 in the Department of pediatrics (pediatric rheumatology clinic and pediatric inpatient department), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. A validated questionnaire was prepared and pre-tested prior to starting the research work. Symptoms of MTX intolerance were included in the questionnaire from MTX intolerance severity score (MISS) questionnaire; a highly sensitive and specific tool for the diagnosis of MTX intolerance [11]. But instead of scoring; only frequency of symptoms were calculated for both the group. Ethical clearance was taken from the Institutional Review Board of BSMMU (No. BSMMU/2020/4832 Date: 21-03-2020).

Newly diagnosed JIA patients fulfilling ILAR criteria, between 1 to 16 years of age attending pediatric rheumatology clinic and inpatient department of pediatrics, BSMMU who would receive treatment with methotrexate (MTX) from the attending pediatric rheumatologists were included as study population by purposive sampling. Children who received other DMARDs (disease-modifying anti-rheumatic drugs) with similar side effects before the initial visit, and children with any systemic co-morbidities including: chronic liver disease, chronic renal disease, tuberculosis, a history of chronic or recurrent serious infective diseases and opportunistic infections were excluded from the study.

Informed written consent was taken from all participants or parents/caregivers after an informal assessment in the clinic. Data were collected by using the structured questionnaire containing demography of the patient, clinical history and examination findings, Laboratory investigations and monitoring parameters of drug toxicity.

Forty diagnosed cases of JIA, who were prescribed MTX were divided in 2 groups alternately (Group A and Group B). MTX was given once weekly, by sub cutaneous route at a dose of 15 mg/square meter body surface area to all the patients (Group A and Group B). Children who received folinic acid were included in group A and those who received folic acid were included in group B. Folinic

acid (Tablet Biofol 5 mg, Incepta Pharmaceuticals Ltd.) was given orally in a single weekly dose (25% - 50% of the MTX dose, corresponding to 2.5 - 7.5 mg) 24 hours after MTX injection. Folic acid (Tablet Folison 5 mg, Jayson Pharmaceuticals Ltd.) was given orally once weekly (not more than 50% of MTX dosing) 48 hours after MTX. As bridging therapy, naproxen (10 mg/kg/day) was added to both the groups along with MTX.

All study subjects were evaluated by the physician at baseline and subsequent follow-ups at the 6th and 12th weeks. The effect of folinic acid to alleviate the side effects of MTX was evaluated in each patient by comparing the number of episodes of hepatotoxicity and gastrointestinal toxicities at follow up visits and compared with baseline. The influence of folinic acid and folic acid on the clinical efficacy of MTX was evaluated in each patient by JADAS 27 [12]. A JADAS-27 score of more than 8.5 were indicative of high disease activity, 3.9 to 8.4 as moderate and a score below 3.8 indicated low disease activity.

Blood samples were collected from the patients by venipuncture for the following baseline laboratory tests: Complete Blood Count (CBC) with Erythrocyte sedimentation rate (ESR), Serum Alanine aminotransferase (ALT), Serum creatinine, routine and microscopic examination of urine at base line, 6th and 12th weeks. Appropriate statistical tests (Chi-square test, t test) were applied for data analysis. A P-value less than 0.05 were considered as significant at 95% confidence interval (95%CI).

3. Result

A total number of 40 JIA patients were taken as study population in two groups (A and B). Age, gender and disease duration were matched between the 2 groups, as there was no significant differences among these parameters.

In Table 1, it is shown that there was significant improvement of total scores of JADAS-27 at 6th and 12th weeks from the baseline in both the groups.

The disease activity was high at baseline and 6th week and moderate at 12th week in both the groups. Reduction of disease activity (evidenced by the mean JADAS score) was more in Group A, compared to group B at both the visits though not significant (Table 2).

Some of the laboratory parameters improved significantly including hemoglobin percentage and ESR in both the groups and neutrophil and lymphocyte count in Group A. Mean Serum ALT decreased from baseline to 12 weeks in both the groups but significantly in folic acid group.

In the Group A, 10% and 15% of patients complained of nausea in the 6th and 12th week respectively and only 5% of patients had vomiting at both the visits. On the other hand, in the group B, significantly higher number of patients (70% and 95%) had nausea in the 6th and 12th week respectively. Vomiting was present in 20% and 90% of patients in the 6th and 12th week respectively in Group B. Restlessness, crying, and irritability was found more in group B at 12 week. All the side effects were significantly higher in Group B. Refusal of MTX was observed in 5% in 6 weeks and 10% in 12 weeks, only in group B (Table 3, Table 4).

Table 1. Changes of JADAS-27 score from baseline to follow up in Group A and Group B (n = 20 + 20).

	Baseline	At 6th week	Improvement (%)	Baseline vs 6th week (p value)	At 12th week	Improvement (%)	Baseline vs 12th week (p value)
Group A (n = 20)	27.35 ± 9.34	13.58 ± 8.82	50.35%	<0.001*	4.48 ± 3.89	83.62%	<0.001*
Group B (n = 20)	27.58 ± 7.72	14.90 ± 7.33	45.98%	<0.001*	5.63 ± 5.65	79.59%	<0.001*

Data were expressed as mean ± SD; Paired t-test within groups, *significant; Group-A: Received Tab. Folinic acid once weekly; Group-B: Received Tab. Folic acid once weekly.

Table 2. Comparison of JADAS-27 score between Group A and Group B (n = 20 + 20).

JADAS-27 score	Group A (n = 20)	Group B (n = 20)	p value
At baseline	27.35 ± 9.34	27.58 ± 7.72	0.934^{ns}
At 6^{th} week	13.58 ± 8.82	14.90 ± 7.33	0.608^{ns}
At 12^{th} week	4.48 ± 3.89	5.63 ± 5.65	0.456^{ns}

Data were expressed as mean ± SD; Unpaired t-test was done, ns= not significant; Group-A: Received Tab. Folinic Acid; Group-B: Received Tab. Folic acid.

Table 3. Changes of laboratory findings from baseline to follow up in both groups (n = 20 + 20).

	Baseline	At 6th week	P Value	At 12th week	P Value
Hemoglobin (g/dl)					
Group A (n = 20)	9.47 ± 1.99	10.34 ± 1.80	0.179	11.00 ± 1.58	0.009*
Group B (n = 20)	9.79 ± 1.54	10.57 ± 1.47	0.004*	11.13 ± 0.73	0.001*
ESR (mm in 1^{st} hr)					
Group A (n = 20)	86.50 ± 26.71	54.55 ± 34.00	0.003*	34.80 ± 24.38	<0.001*
Group B (n = 20)	71.35 ± 35.07	37.85 ± 28.37	<0.001*	27.80 ± 15.36	<0.001*
Total WBC count ($\times 10^9$/L)					
Group A (n = 20)	14.23 ± 4.05	12.36 ± 5.63	0.094	12.35 ± 7.46	0.162
Group B (n = 20)	11.61 ± 3.90	10.33 ± 2.71	0.096	16.72 ± 2.56	0.388
Neutrophil (%)					
Group A (n = 20)	69.00 ± 11.00	60.05 ± 16.79	0.006*	60.70 ± 20.42	0.046*
Group B (n = 20)	63.00 ± 13.39	60.95 ± 13.60	0.605	54.65 ± 11.82	0.21

Continued

Lymphocytes (%)					
Group A (n = 20)	22.85 ± 7.22	32.70 ± 14.39	0.003*	32.10 ± 17.29	0.014*
Group B (n = 20)	30.65 ± 11.86	31.40 ± 7.63	0.820	34.50 ± 10.58	0.252
Platelet count ($\times 10^9$/L)					
Group A (n = 20)	472.45 ± 135.05	605.75 ± 738.83	0.415	436.30 ± 128.05	0.380
Group B (n = 20)	534.40 ± 194.74	509.00 ± 150.12	0.635	455.72 ± 167.77	0.141
Serum ALT (U/L)					
Group A (n = 20)	28.95 ± 31.21	50.60 ± 131.77	0.487	15.45 ± 7.90	0.072
Group B (n = 20)	22.55 ± 15.51	16.35 ± 5.58	0.063	13.45 ± 5.53	0.028*

Data were expressed as mean ± SD; Unpaired t-test between groups and Paired t-test within groups, *significant.

Table 4. Presence of MTX related side effects between Group A (n = 20) and Group B (n = 20).

Adverse effects		Group A (n = 20)	Group B (n = 20)	p value
Nausea	6 weeks	2 (10.0%)	14 (70.0%)	<0.001*
	12 weeks	3 (15.0%)	19 (95.0%)	<0.001*
Vomiting	6 weeks	1 (5.0%)	4 (20.0%)	0.151
	12 weeks	1 (5.0%)	18 (90.0%)	<0.001*
Abdominal pain	6 weeks	0 (0.0%)	1 (5.0%)	0.311
	12 weeks	0 (0.0%)	3 (15.0%)	0.072
Restlessness	6 weeks	0 (0.0%)	1 (5.0%)	0.311
	12 weeks	0 (0.0%)	6 (30.0%)	0.008*
Crying	6 weeks	0 (0.0%)	3 (15.0%)	0.072
	12 weeks	0 (0.0%)	11 (55.0%)	<0.001*
Irritability	6 weeks	0 (0.0%)	1 (5.0%)	0.311
	12 weeks	0 (0.0%)	5 (25.0%)	0.017*
Refusal to MTX	6 weeks	0 (0.0%)	1 (5.0%)	0.311
	12 weeks	0 (0.0%)	2 (10.0%)	0.147

Data were expressed as frequency and percentage; Chi-square test was done, * = significant.

4. Discussion

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood [1]. Treatment with non-steroidal anti-inflammatory drugs, steroids, and disease-modifying anti-rheumatic drugs (DMARD) had been the backbone in the management of JIA for many years. Methotrexate (MTX) is currently the most effective and commonly used DMARD in the treatment of JIA. But due to its side effects, compliance is often low and thereby improvements of disease activities are often guarded. It is reported that approximately 37% of adult patients with rheumatoid arthritis discontinued treatment with MTX within 1 year because of its toxicity [13]. For the first time in our country, the present study aimed to assess the efficacy of folinic acid in comparison to folic acid in reducing the side effects of MTX without affecting its efficacy.

In the present study, the mean hemoglobin concentration at baseline was less than 10 g/dl in both the Groups. Presence of anemia in all the cases may be explained by the fact that most of the JIA cases in this cohort were sJIA and polyarticular JIA, with high disease activity. And anemia is common in both the sub-types. In the 6th and 12th weeks, mean hemoglobin increased significantly in both groups as the disease activity decreased.

Acute-phase reactant like ESR refers to proteins synthesized in the liver that increase in plasma during inflammatory conditions like JIA. In the present study, mean ESR was high in both the groups at the initial visit and decreased significantly at subsequent follow-ups. These results support the strong association of ESR with JIA disease activity. Our results are consistent with the studies done by Wu *et al.*, where the higher disease activity state of JIA patients had higher ESR [14].

A raised S.ALT level reflects hepatic dysfunction which is an important indicator of MTX toxicity. In this study, significant elevations of transaminase levels were not observed in any group. Rather, S ALT decreased in both the groups at 12th week which was significant in Group B. A similar study done in the Netherlands did not find any significant difference in ALT values between folinic and folic acid groups [15].

The result of our prospective study suggests that folinic acid supplementation significantly reduces the frequency of MTX related side effects in comparison to folic acid. Therapeutic benefits of MTX were also more in folinic acid group than folic acid group. Different studies focusing on adult rheumatoid arthritis patients found variable results [16] [17] [18] [19] [20].

Ravelli *et al.* in a retrospective, non-controlled study in Italy, enrolling 43 JIA patients aged 1.2 - 16 years, found folinic acid supplementation led to a significant reduction in the most common side effects of MTX including hepatic and gastrointestinal toxicity, without affecting the clinical efficacy of MTX [6]. Ravelli *et al.* used a lower dose of folinic acid which was about 25% - 50% of that of MTX, given 24 hours after MTX therapy. Our protocol was similar to that of Ravelli *et al.* Fisher *et al.* in Denmark suggested from their study that folinic acid may be

considered, when side effects of MTX in routine care cannot be managed effectively with folic acid supplementation [10].

All the study participants in this cohort had severe disease activity at the initial visit and 6th week due to severe manifestations at presentation. Islam *et al.* in their study also reported severe manifestations of disease by JIA patients at presentation from our country [21]. Patients in both the groups had moderate disease activity at 12th week. There was significant improvement in the 6th and 12th weeks from the baseline in both the group and improvement was more in group A compared to group B.

The most common side effects of MTX are nausea, vomiting, irritability, and abdominal pain. In the present study, Group A children had only nausea and vomiting. Additionally, Group B cases complained of crying, irritability, restlessness, abdominal pain and refusal to take MTX. Significant differences were found in symptoms including nausea, vomiting, restlessness, crying and irritability in between the 2 groups. More side effects were observed in the folic acid group which indicates folinic acid worked more effectively in reducing the toxicity of MTX.

In the present study, though not significant but higher number of patients in group A (25%) did not have any disease activity at the 12th week of follow up than group B (15%). This result may indicate that folinic acid is more efficacious in reducing the side effects of MTX and thereby improving the compliances. Folinic acid causes no potential side effects.

To the best of our knowledge, no trials has been done in our country, comparing the efficacy of folic and folinic acid in reducing MTX toxicity. This pioneer study, found that children in the folinic acid group had significantly fewer side effects, suggesting that folinic acid supplementation can be more effective in reducing side effects of MTX than folic acid, without influencing the therapeutic benefit and helps in better compliance, and thereby reduces disease activity. The cost ratio of folic acid: folinic acid varies in different countries. In our country, cost of folic acid is much lower to that of folinic acid (BDT 0.50 Vs. BDT 9.0; 1 USD = BDT 100 roughly). But benefits in reducing side effects and thereby better compliance resulting to decrease in disease activity might over weigh the cost. So, folinic acid may be supplemented in routine care with MTX or it may be considered when side effects cannot be managed effectively with folic acid supplementation.

5. Conclusion

The present study shows, children in the folinic acid group had only nausea and vomiting which was also significantly lower than folic acid group. On the other hand, the folic acid group, in addition to nausea and vomiting had other symptoms including restlessness, crying, irritability, abdominal pain, and refusal to MTX. So, it may be concluded that folinic acid supplementation is more effective in reducing side effects of MTX than folic acid without influencing the therapeu-

tic benefit which might help in better compliance, and thereby reduced disease activity. So, folinic acid may be supplemented in routine care with MTX or it may be considered when side effects cannot be managed effectively with folic acid supplementation.

6. Recommendations

Though limitations of the present study including small sample size, short duration and single centered study were there, however, from the results and observation of this study, following recommendations can be made:

1) Further study should be done with larger sample size, involving multiple centers for giving definite recommendations.

2) Longer duration study should be undertaken to assess sustained remission and further side effects.

3) A cross over study may be done by giving folinic acid in patients who complain of vomiting in spite of getting folic acid.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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