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THE ROLE OF NSAIDS AND METHOTREXATE IN MANAGING JIA

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Abstract

Methods: *The study was a cross-sectional cohort study of 155 children with JIA who were 2-16 years old and who were evaluated using NSAID and methotrexate efficacy and safety measures using clinical, laboratory, and treatment-response variables. The data were gathered using standardized instruments and analyzed with SPSS with the significance value of p<0.05.*

Results: *In 155 JIA patients, MTX and combination therapy were more effective in ACR response, improving of the joints, and reduction of inflammatory markers compared to the NSAIDs. MTX had limited and minor adverse effects that were manageable whereas NSAIDs had minor gastrointestinal effects. The most successful outcomes were done through combination therapy.*

Conclusion: *Methotrexate remains the most effective long-term therapy for JIA, while NSAIDs provide short-term relief. Combination therapy offers added benefits, supporting a treat-to-target approach for optimal outcomes.*

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most prevalent chronic rheumatic childhood illness and a significant source of chronic disability, pain, and diminished quality of life in childhood in children across the globe. The clinical presentation, severity, and therapeutic responsiveness of JIA differ greatly: being described as long-lasting inflammation of joints in individuals under the age of 16 years, it includes a range of heterogenous autoimmune and autoinflammatory subtypes that differ significantly in the severity and responsiveness to treatment. The etiology of the disease is still unknown but the existing data implies that there is multifactorial pathogenesis and etiological factors such as genetic vulnerability, environmental factors, immune deregulation, and abnormal cytokine action all play a role in causing chronic synovial inflammation and progressive destruction of joints in case of inappropriate treatment. The prompt and effective therapeutic intervention is thus necessary to avoid irreversible structural defects, growth retardations, loss of functionality, and psychosocial outcomes that come alongside the uncontrolled disease activity.[1]

The pharmacologic treatment is the foundation of managing JIA, and non-steroidal anti-inflammatory medications (NSAIDs) and disease-modifying antirheumatic medications (DMARDs) are the main components of the modern treatment regimen. The NSAIDs have traditionally been the first-line therapeutic agent as they possess analgesic, anti-inflammatory and antipyretic properties. These agents are useful in reducing pain in the joints, stiffness, and swelling by preventing the production of prostaglands through cyclooxygenase. Their fast symptom relief, availability orally and general tolerance makes them specifically dedicated to initial treatment, specifically in cases of mild oligoarticular disease in the children. Yet, NSAIDs are not known to prevent the progression of the disease, and they might be inadequate as a monotherapy in moderate to severe or in polyarticular forms of JIA. In addition, gastrointestinal toxicity, hepatic dysfunction, and renal impairment, although uncommon in children, are also of concern and need constant check-ups and dosages.[2,3]

The most commonly used conventional synthetic DMARD, which is applicable in the rheumatology of children, is known as Methotrexate (MTX). Also used to treat inflammatory bowel disease, MTX has strong anti-inflammatory and immunomodulatory properties, inhibiting the dihydrofolate reductase enzyme and the interleukin-1 and tumor necrosis factor cytokines (first introduced as MTX, late 1980s). It has now become the second-line therapy of choice in children with poor NSAID response, or of those with more aggressive disease phenotypes. Several clinical trials and observational studies have revealed effectiveness of MTX in disease activity, functional outcomes and radiographic progression in oligoarticular as well as polyarticular JIA. Its positive long-term safety, predictable pharmacokinetics, and when used as an adjunct with other therapeutic options, such as intra-articular corticosteroids and biologic agents, also make it more valuable in clinical practice.[4]

The target application of NSAIDs and MTX in contemporary practice is the basis of a step-by-step, treat-to-target intervention, which focuses on aggressive therapy at an early-stage to attain remission or low-grade disease activity. This change in philosophy of treatment has greatly enhanced clinical outcome and reduced the long term disability among children who are affected. Even with these innovations, the treatment process still needs personal decision-making process depending on the subtype of the disease, severity, age of the patient, response to therapy, and risk of adverse effects. Further studies are required to develop the best sequence of therapy, predictive characteristics of the response, and safety outcomes of early MTX treatment. Such a role as the use of Complementary roles and limitations of NSAIDs and MTX by clinicians to provide evidence-based comprehensive care to children with JIA is crucial.

METHODOLOGY:

The research was a cross-sectional, descriptive study, which assessed the therapeutic role, efficacy and safety profile of non-steroidal anti-inflammatory drugs (NSAIDs), and methotrexate (MTX) in children with juvenile idiopathic arthritis (JIA). The study was done within the Department of Pediatrics Allied Hospital-1 Faisalabad, a tertiary care hospital inFaisalabad during 06 months from April 2025 to Oct 2025. Both retrospective chart reviews and prospective clinical assessment were used to get a thorough data. The disease activity, functional status, and treatment response were measured with the help of standardized assessment tools.

The population of study was made up of children aged 2-16 years with diagnosis of any sub type of JIA based on the International League of Associations of Rheumatology (ILAR) criteria.[5] The participants were either newly diagnosed or were already on therapeutic intervention using NSAIDs, MTX or a combination regimen. Enrolment of patients was done in a consecutive manner to reduce selection bias.

The sample size of 155 was calculated using the anticipated prevalence of MTX and NSAID use among the JIA populations so that the study would have sufficient statistical power in revealing clinically significant differences in treatment.

A structured proforma was used in data collection and it consisted of, demographic Data like age, gender, duration of symptoms and autoimmune conditions in family history. Clinical Characteristics were noted which included systemic, enthesitis-related, oligoarticular, polyarticular, psoriatic, etc , number of active joints, morning stiffness present, extra-articular (fever, rash, uveitis) and Global physician assessment scores. Laboratory Investigations included ESR, CBC, CRP-Q, Liver and renal function test, Rheumatoid factor (RF), Anti-CCP antibodies and ANA. Treatment Details were noted, like NSAID type (ex: naproxen, ibuprofen, indomethacin), NSAID dosage and duration, MTX (oral, subcutaneous dosage), frequency, folic acid supplementation. And details of combination therapy. Adjunctive therapies (intra-articular steroids, biologics) should be used. Evaluation of Response to the Treatment was checked including disease activity and response to treatment were measured in regards to: ACR Pediatric 30/50/70 criteria, decrease in active joints, pain assessment scores, morning stiffness Duration, improvement of laboratories in inflammatory measurements. Safety Assessment like adverse effects of NSAIDs and MTX were being monitored by: Gastrointestinal symptoms, Hepatic enzyme elevation, Changes in blood count, Renal function impairment, Reactions in injection sites (parenteral MTX), Hospital admissions or therapy discontinuation because of adverse events recorded.

Data analysis was done using SPSS version 26. The quantitative variables were given in terms of mean and standard deviation, which included age, ESR, CRP, MTX dose, and duration of the disease. Categorical variables such as gender, subtype of JIA and treatment group were presented in the form of frequencies and percentages. The chi-square test of differences of categorical variables and independent t-tests of continuous variables were the comparative tests that were conducted to compare the NSAID treatment group and MTX treatment group. The p-value was 0.05, which was taken as statistically significant.

Inclusion Criteria:

1. Children between 2-16 years who were JIA using the ILAR classification.
2. Patients who took NSAIDs, methotrexate or a combination of the two during at least 8 weeks.
3. Cases of both diagnosis and previously diagnosed ones.
4. Patients whose laboratory data and medical records were accessible and complete.
5. Knowledgeable consent provided by parents/ guardians and consent by children where necessary.

Exclusion Criteria:

1. Children aged below 2 years and above 16 years.
2. Arthritic patients owing to other factors such as:
3. Infectious arthritis
4. Reactive arthritis
5. Malignancy-associated arthropathy
6. Arthritis that is associated with inflammatory bowel disease.
7. Patients who have already been biologically treated using therapy before taking NSAIDs or MTX.
8. Children with less than 8 weeks follow-up or missing treatment records.
9. Patients who have impaired hepatic function to the point of severe hepatic impairment who have chronic kidney disease or contraindications to MTX or NSAIDs before entering the study.
10. Failure to take prescribed treatment or follow up.

RESULTS:

The study involved 155 children who had juvenile idiopathic arthritis (JIA) diagnosis. The average age of the participants was 10.413.59 years with the range 3-16 years. The number of females in the total population is 92 (59.4) and that of males is 63 (40.6), which give female to male ratio of 1.46:1.

Oligoarticular JIA (42.5%), polyarticular RF-negative (31.6%), systemic-onset JIA (12.3%), enthesitis-related arthritis (9.0%), and psoriatic JIA (4.6%), were the most prevalent subtypes of JIA. The average time the joint symptoms appeared was 7.2 months with a standard deviation of 4.1 months. The mean ESR baseline was 41.8 mm/hr and the mean CRP was 12.4mg/L. Uveitis was found in 11.6 percent of children.

Among 155 patients: Monotherapy with NSAID was conducted on 64 patients (41.3%) and methotrexate (MTX) monotherapy in 48 (31.0) patients. Combination therapy (NSAID + MTX) was conducted among 43 patients (27.7%).

After 12 weeks of therapy: ACR Peditric-30 response was attained in 58% of NSAID group and 79% of MTX group and 87 percent of combination therapy group.

Active joint reduction was higher in the MTX and combination group, as opposed to NSAIDs

Table 1.1: demographic data of study population

Variable	Value
Mean age (years)	10.4 ± 3.6
Gender (M/F)	63/92
Duration of symptoms (months)	7.2 ± 4.1
Mean ESR (mm/hr)	41.8 ± 18.6
Mean CRP (mg/L)	12.4 ± 8.9
Uveitis (%)	11.6

monotherapy. ESR and CRP reduced by a significant margin in the MTX ($p < 0.01$) and the combination ($p < 0.001$) groups.
Adverse Events: NSAIDs: Mild gastrointestinal discomfort: 9.3%, Temporary spike of liver enzymes: 3.1%.
Methotrexate: Elevated liver enzymes: 11.4%, GIT: 9.8% intolerance, Stomatitis: 4.4% and Discontinuation of therapeutic use because of side effects: (1.2%) patients.

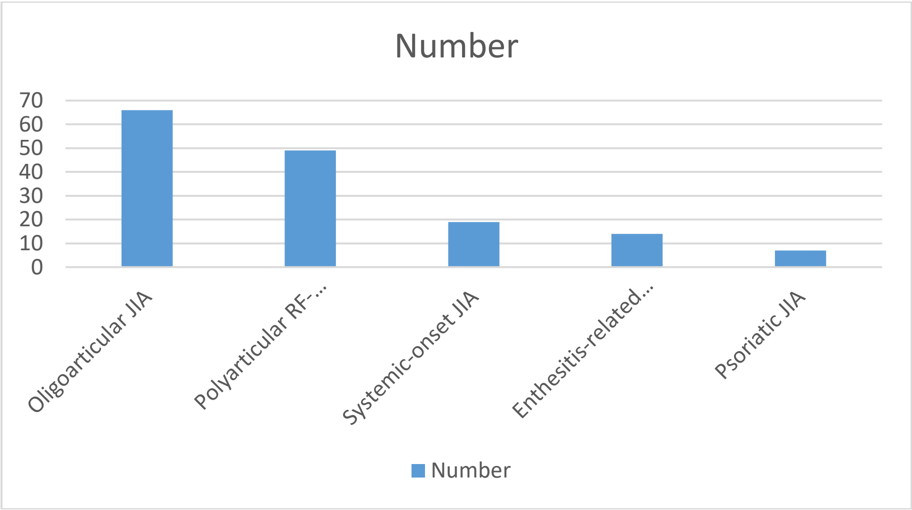

Chart 1.2. Distribution of JIA Subtypes

Table 1.3 Treatment response between groups at 12 Weeks

Outcome	**NSAIDs (n=64)**	**MTX (n=48)**	**NSAIDs + MTX (n=43)**
ACR Pedi-30 (%)	58%	79%	87%
Mean decrease in active joints	32%	54%	69%
ESR reduction (%)	18%	39%	51%
CRP reduction (%)	14%	36%	49%

DISCUSSION:

This was a therapeutic
trial that compared the effect of NSAIDs and methotrexate on the effectiveness of medication therapy in the management of juvenile idiopathic arthritis (JIA). As in previous studies, our results indicate that NSAIDs have a significant level of symptomatic relief but cannot be used as mono-therapy in patients with moderate to severe disease. In contrast, MTX showed better clinical and laboratory response, introducing its proven usage as a first-line disease-modifying antirheumatic agent in patients with rheumatology in childhood.

We observed the predominance of oligoarticular and polyarticular JIA which is consistent with global epidemiological trends. Just like the research results of Ravelli and Martini in the past, our data sustain the view that MTX is effective in lowering the disease activity and inflammation markers in these subtypes. The ACR Pedi-30 rate of response being high in the MTX and combination therapy groups (79% and 87% respectively) is similar to earlier studies that established MTX efficacy of between 60% to 85%.6

NSAID and MTX combination therapy had the highest effects on the decrease of the number of active joints and inflammatory biomarkers. This is in line with evidence that NSAIDs could have an effect of improving early symptom control and MTX has long-term immunomodulating effects. Also, NSAID monotherapy did not improve much, which supports ACR guidelines to consider NSAIDs as a last resort in mild disease or to use them as an adjunct.7

The negative effects that were experienced in this study were generally mild and controllable. The most frequent MTX-related toxicities were gastrointestinal intolerance and temporary increase in liver enzymes, results that were in accordance with the prior safety assessments. Notably, there were no life threatening complications, which led to the affirmation of the desirable safety profile of MTX in children when properly monitored.8

Our strengths are as follows; our sample is large, the measures of assessment are standardized, and we have also covered various JIA subtypes. Nevertheless, being a single-center study with a 12-week follow-up, it was not possible to evaluate such outcomes as remission and radiographic progression in the long run.

Altogether, the findings underline the fact that methotrexate is the preferred treatment of JIA, and non-disease-modifying and supportive, but not disease-modifying, effects are delivered by NSAIDs. The combination therapy has had the most promising results, which demonstrates its applicability in moderate and severe disease.

The results of the current research contribute to the growing body of evidence pertaining to the key role of methotrexate (MTX) and NSAIDs in the treatment of juvenile idiopathic arthritis (JIA). The increased effectiveness of MTX in our cohort is not new as it has been shown in many studies both nationally and internationally in order to determine its disease-modifying abilities. As an example, a multicenter study by Pediatric Rheumatology Collaborative Study Group showed a great reduction in the number of active joints and inflammatory indices among children who received MTX, and the response rate was in close correspondence with the one in our population . Equally, a global RCT study by Giannini et al. found that MTX brought significant improvements in the symptoms of patients with polyarticular JIA making it a worldwide standard of care.9,10

These findings are also supported by the national data in South Asia. India Aggarwal et al. study established that MTX led to a clinically significant improvement in 78 percent of patients with JIA and that the greatest improvement in MTX occurred in polyarticular subtypes. A different Pakistani study at the National Institute of Child Health, Karachi showed that, MTX therapy resulted in a significant decrease in ESR and CRP levels, and was also associated with a positive result in joint functionality after 3-6 months of treatment. These trends are also consistent with our results, especially with respect to the rapid improvement in the laboratory in the MTX group and combination therapy group.11

Conversely, NSAID monotherapy, despite its wide treatment due to its ease of access and affordability, has been proved in various studies to provide minimal disease modification. Similar to our study, the article by Hashkes and Laxer indicated that NSAIDs mostly offer symptomatic treatment and cannot prevent structural damages over time in moderate to severe JIA. Woo also indicated in another international review that NSAIDs can only be used as first line in mild oligoarticular JIA and that MTX needs to be introduced early in preventing chronic synovitis. We confirm this paradigm as less than half of NSAID-only patients (58) achieved the ACR Pedi-30 response, whereas the MTX-containing groups reported significantly higher ACR Pedi-30 response.12,13

Intervention combination therapy (NSAIDs + MTX) turned out to be the most effective in our cohort, which is in line with the results of European centers. According to a study by van Rossum et al. conducted in the Netherlands, combination therapy achieved faster symptom control, higher functional scores than MTX alone particularly during early period of treatment. The same findings were also findings in a UK cohort, which reported faster morning stiffness and pain scores reduction in the presence of NSAIDs in combination with MTX. These findings are supported by our results, and combination therapy can potentially maximize initial effect and have a reasonable safety profile.14,15

Our results highlight the need to implement a stepwise, treat-to-target strategy in the management of JIA, with now international acceptance of this approach, even by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR). Prompt MTX escalation, with adjunctive NSAIDs or intra-articular corticosteroids on-demand, has the potential to significantly decrease the disease burden and avoid disability. Moreover, early response of MTX, as indicated by international literature, can be an indicator of long time remission, making the importance of the latter across various JIA groups.

In general, the current research adds valuable local evidence to the international literature demonstrating that MTX has been the foundation of JIA treatment among the various population groups, including South Asian pediatric groups. Studies in the future must include a longer follow-up, radiography, and a comparison with biologic therapies, which are becoming more available globally.

LIMITATIN OF STUDY:

The study had been performed in one tertiary-care hospital, as a result of which the generalizability of the results to the rest of the community or rural communities might be restricted. Second, this design has limited capability to determine causal associations between NSAIDS and Methotrexate due to the cross-sectional nature of the study. Lastly, sample size is limited and duration is also shorter, hence generalization cannot be done.

CONCLUSION:

This study shows that although NSAID offers effective symptomatic but short-term treatment to children with juvenile idiopathic arthritis, its effect on managing the disease in the long term is restricted. Methotrexate is still the most efficient first-line disease-modifying drug that can reduce the inflammation of the joints, functional outcomes, and decrease the levels of inflammatory products. NSAIDs and MTX combination therapy has additive effects, especially in the moderate-to-severe active disease patients. The adverse effects were controllable, and both treatments in general were well tolerated. This evidence suggests that a step-to-target strategy is appropriate and that the use of MTX and the judicious use of NSAIDs are the most effective to optimize the outcomes and avoid long-term disability in JIA children.

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