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Comparative Study to Assess the Safety and Effectiveness of Methotrexate and Tofacitinib in Patients Diagnosed with Rheumatoid Arthritis

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Abstract **Original Research Article**

***Introduction*:** Rheumatoid Arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints resulting in pain and disability. The prevalence of RA is estimated to be 1% to 2% globally and does not have any ethnic or racial differences. Elevated C-Reactive Protein (CRP) levels in the blood indicate the presence of inflammation and can be used to detect and monitor the disease. Patients with RA tend to have a significant load in association with pain, disability and activity limitation which in turn affects the Health-Related Quality of Life. With a growing rate of RA globally there is a need to assess the safety and effectiveness of drugs and provide a suitable treatment to improve the quality of life of the patients. OBJECTIVES: The goal of the study was to compare the safety and effectiveness of Tofacitinib and Methotrexate in patients diagnosed with Rheumatoid Arthritis. The study also aimed to assess the Health-Related Quality of Life (HRQOL) of patients. ***Methodology*:** This was an observational study conducted in selected Orthopaedic clinics in T. Dasarahalli Bengaluru. All the subjects (n=40) meeting the inclusion and exclusion criteria were briefed about the purpose of the study and the informed consent was obtained. The subject's demographic details and responses were collected. Standard questionnaires, 36-Item Short Form survey (SF-36) to assess the HRQOL and Health Assessment Questionnaire-Disease Index (HAQ-DI) to assess the effectiveness of the drugs were used in all patients. The collected data were entered in Microsoft Excel and appropriate descriptive and statistical analysis was performed. ***Results*:** A total of 40 samples were enrolled in the study based on Inclusion and Exclusion criteria. Out of which 50% of the participants were on Methotrexate (MTX) and the other 50% were on Tofacitinib. Majority of the subjects in the study were women (90%) and men (10%) with mean age 51 and 54 respectively. On comparing the effectiveness of both Methotrexate and Tofacitinib, it was found that the rate of reduction of CRP levels and HAQ-DI was better in Tofacitinib than in Methotrexate. The HRQOL was assessed using SF-36 and the overall average of Tofacitinib and Methotrexate was found to be 56.4 and 61.6 respectively. ***Conclusion*:** From this study, Tofacitinib to be more effective than Methotrexate with regard to its ability to decrease CPR levels. This study also found RA to have a significant impact on the HRQOL of patients and the most affected domain was role limitation due to physical.

Keywords: Rheumatoid Arthritis, C-Reactive Protein, HRQOL, Methotrexate, Tofacitinib, SF-36, HAQ-DI.

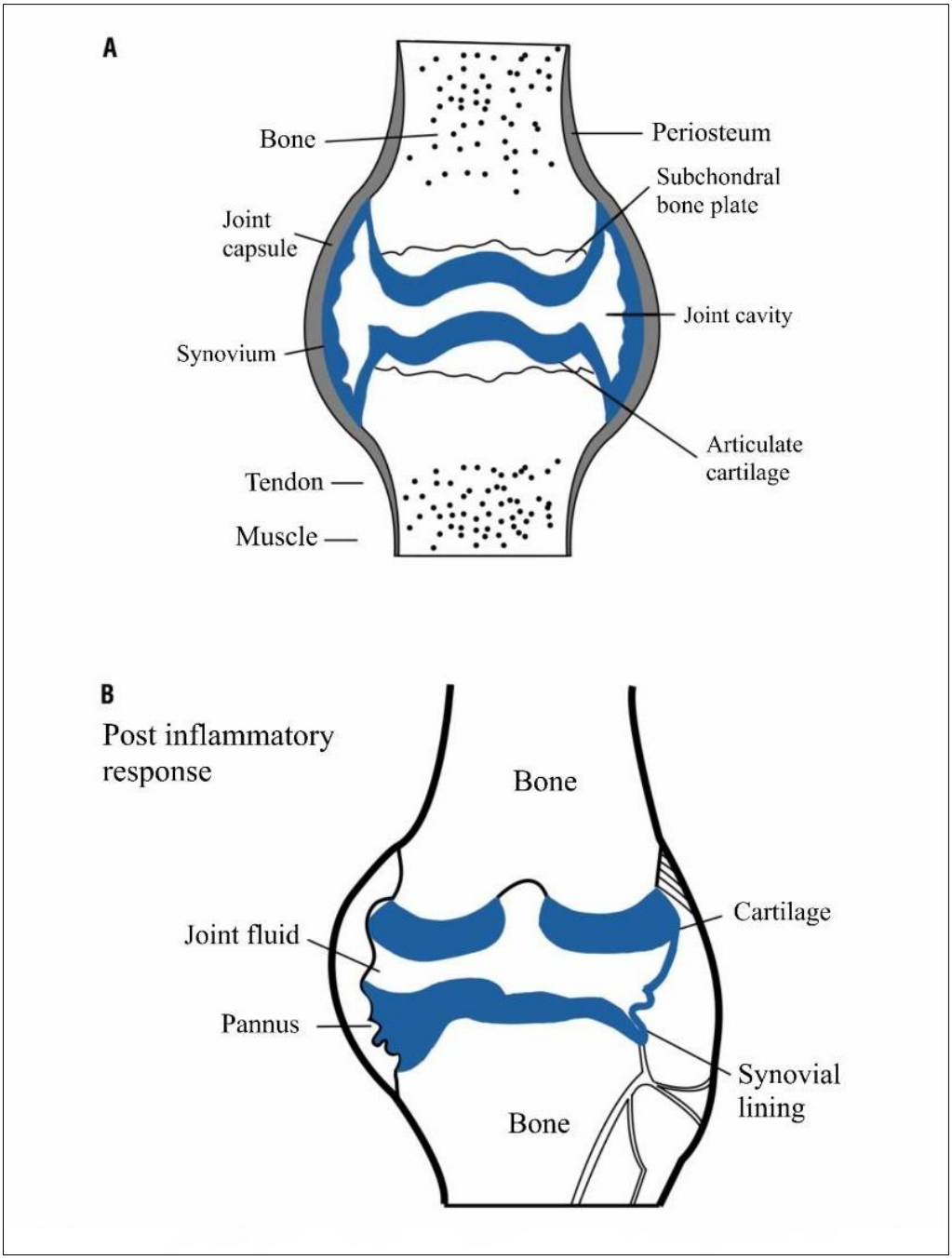
INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune condition of undermined cause, which usually starts with the swelling of the synovial membrane, and eventually results in the destruction of joints and deformities. It is a progressive disease as it affects the skin, eyes, heart, and lungs eventually if left untreated. Extra-articular manifestation is seen in around 40% of the RA population. It is frequently distinguished by morning stiffness lasting more than 30 minutes, fever, weight loss, swollen joints, and tenderness. Extra-articular and symmetrical joint involvement makes RA different from other types of arthritis.

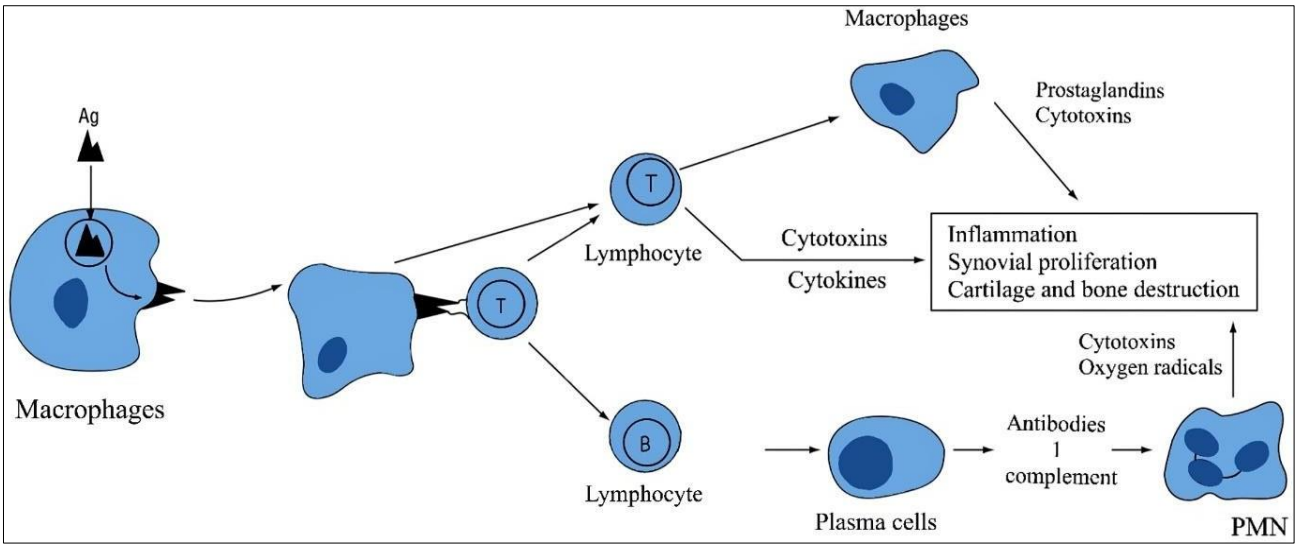
The prevalence of RA is estimated to be 1% to 2% globally and does not have any racial predilections. It affects about 1.5 million people in the United States and 0.92% of the Indian adult population. The incidence of the disease is 3-4 times higher in women compared to

men that ranges from 0.5% to 3.8% and 0.15% to 1.37% respectively among the Indian population. RA is largely influenced by both genetic and environmental factors. People with variations in the Human Leukocyte Antigen (HLA) genes are susceptible for RA (HLA-DRB1*04, HLA- DRB1*10 and HLA-DRB1*01). Female sex, family history of RA, bacterial infections, and tobacco smoke exposure are the other risk factors for RA.

In the case of RA the body can no longer distinguish self from non-self and attacks the synovial tissue and other connective tissues. Patients with RA appear to have T-helper cell activity in synovial tissue in higher amounts, activation of T-cells and macrophages releases factors that promote tissue destruction, resulting in increased blood flow, cellular invasion of synovial fluid and joint fluid. Seropositive patients tend to have higher disease activity compared to patients with seronegative patients. Early diagnosis is essential for the most effective therapy outcomes, particularly in individuals who have well-known risk factors for poor outcomes, such as high disease activity, autoantibodies, and early joint destruction.



Comparison between health joint and RA



Pathogenesis of RA

Management program for RA involves not just pharmacological but also nonpharmacologic interventions, which include patient education, psychosocial interventions, weight management, and appropriate rest. Dietary modification also play an important role in controlling the disease such as avoidance of processed carbohydrates like white flour and white sugar, and saturated fats. Clinical remission and improved quality of life are the primary goals of treatment for inflammatory diseases. Medications in addition to symptom control, also retard joint damage and improve functions.

Methotrexate (MTX), Disease-Modifying Anti-Rheumatic Drug (DMARD), is the first-line treatment for RA. It suppresses inflammation and immune reactions by inhibiting aminoimidazole4-carboxamide ribonucleotide which increases adenosine levels. The discontinuation rate of MTX in patients due to toxicity was about 10-37% and most of the patients had at least one adverse event. Most common adverse events reported are gastrointestinal events (52-65%), elevated liver enzymes, and infections. Janus kinase inhibitors (JAKi), especially Tofacitinib, are the alternatives given to patients who have had increased adverse effects or inadequate response to MTX therapy. Tofacitinib reduces inflammation by blocking JAK1, JAK2, and JAK3. Similar to Methotrexate, Tofacitinib is also found to have an increased discontinuation rate (6.9%) due to adverse drug events, including infections (Urinary tract and Herpes zoster), malignancies, increased blood creatinine, etc. Since these drugs are given for long-term treatment, it is necessary to monitor for the safety and effectiveness of the drugs. The effectiveness of drugs can be measured by evaluating C-reactive protein (CRP) levels which is a marker for systemic inflammation in RA, Higher CRP levels are linked with greater disease activity. Despite the severity of the disease, adverse drug reactions/adverse events also have an impact on the patient's Quality of life resulting from the individual burden of physical and mental distress.

In this study, 'Short Form-36' (SF-36) questionnaire was used to assess the HRQOL. It consists of a total of 36 questions which are categorized into 8 domains: Physical functioning, Physical health-related role restrictions, role restrictions caused due to emotional issues, Energy, emotional stability, and social interaction, Health in general and pain. These are further subdivided into physical component summary, (physical functioning, role physical limitation, pain and general health), mental component summary (social functioning, role limitation due to emotional problems, emotional well-being and energy) and overall HRQOL. Health Assessment Questionnaire-Disease Index (HAQ-DI) is used in this study to assess the health state and functionality in patients receiving MTX and Tofacitinib respectively. It consists of 20 questions that measure disability, discomfort, and pain. Dressing, getting up, eating, walking, maintaining hygiene, reaching and gripping, and common activities are the eight areas that are used to evaluate a person's level of disability. The presence of pain and the degree to which it is experienced are the two factors that combine to form discomfort. RA is incurable and is one of the leading causes for disability worldwide. With the growth of RA population, there is a need to encourage intervention to improve the quality of life and mental health. By comparing the safety and effectiveness of MTX and Tofacitinib, it may help in making better choices of treatment to enhance the Health-related Quality of life of patients diagnosed with RA.

MATERIALS AND METHODS

Study Design: This is a community based Cross-sectional study (prospective).

Study Duration: 6 Months

Study Centre: The study was conducted at selected orthopaedic clinics in T. Dasarahalli, Bengaluru District.

Sample size: A total of 40 subjects were enrolled for the study.

Inclusion Criteria

- Subjects willing to give consent.
- Subjects of age 18 years and above.
- Subjects of both the gender.
- Subjects diagnosed with Rheumatoid Arthritis.
- Subjects prescribed with either Methotrexate and Tofacitinib.

Exclusion Criteria

- Individuals not willing to provide information.
- Pregnant and lactating women.

Source of Data

The different sources of data were:

1. One to one interview with study subject.
2. Questionnaire

RESULTS

This study was conducted in selected Orthopaedic clinics in T. Dasarahalli, Bengaluru District. The study was carried out for a period of 3 months, and 40 samples were collected. Out of which 20 samples were on Methotrexate and the other 20 samples were on Tofacitinib.

Age Distribution of Subjects in Methotrexate (Mtx) Group

The mean age of the study population for MTX was found to be 49±9years. Age group 41-50 were in majority accounting for 40% of the subjects and age groups 21-30, 31-40 and 61-70 were minimal in number respectively.

Table 1: Age distribution of subjects in MTX group

Age group	Number of patients	Percentage (%)
18-28	1	5
29-39	1	5
40-50	9	45
51-61	8	40
62-72	1	5

Dose Distribution among Subjects in the Methotrexate Group

Out of 20 samples, 14 of them were taking 10mg MTX once a week (70% of the subjects) and 6 were taking 2.5mg MTX once a week (30% of the subjects).

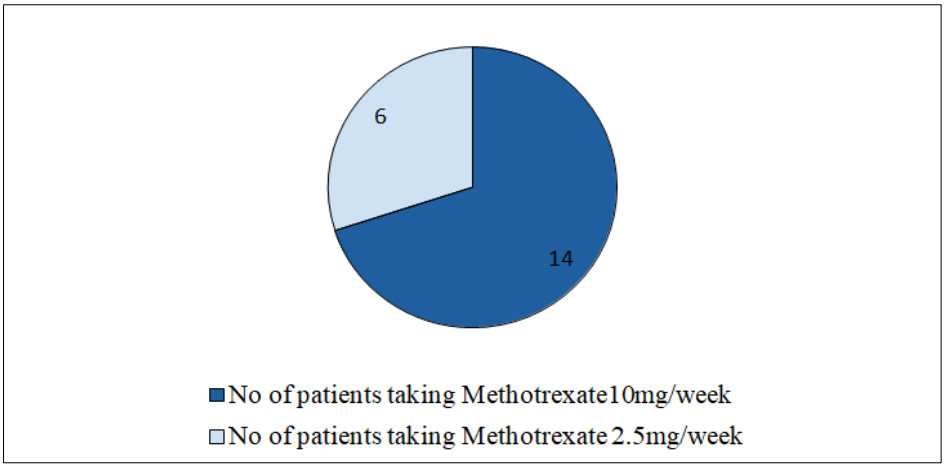


Fig-1: Dose distribution among Methotrexate group

Age Distribution of Subjects in Tofacinitib Group

The mean age of the study population on Tofacitinib was found to be 55±10.3 years. Age group 61 -70 were in majority accounting for 35% of the total population, and age group 31-40 were minimal in number.

Table 2: Age distribution of subjects in Tofacitinib group

Age group	Number of patients	Percentage (%)
18-28	0	0
29-39	1	5
40-50	7	25
51-61	5	25
62-74	7	35

Dose Distribution among Subjects in Tofacitinib Group

Out of 20 samples, 11 of them were on Tofacitinib 10mg twice daily (55%), and 9 of them on Tofacitinib 5mg twice daily (45%).

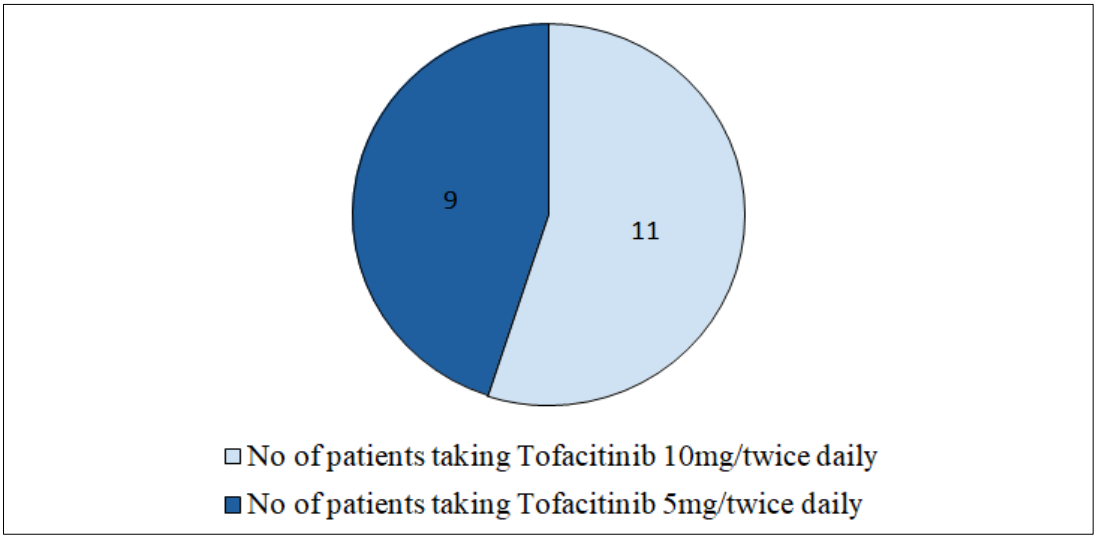


Fig-2: Dose distribution among Tofacitinib group

Comparison of Methotrexate (Mtx) and Tofacitinb with C Reactive Protein

Assessment of Methotrexate

Methotrexate 2.5mg/week and Methotrexate 10mg/week was administered by 30%, 70% of the total subjects respectively. By assessing the C-reactive protein (CRP) levels in both group and by statistically analysis, Methotrexate 2.5mg/week was found to decrease CRP levels much greater than MTX 10mg/week.

Table 3: Comparison of CRP between Methotrexate 2.5mg/week and 10mg/week

METHOTREXATE		
	2.5mg/week	**10mg/week**
Number of patients	6	14
Initial		
Mean	9.26±1.78	12.15±2.03
After 3 months		
Mean	8.53±1.81	10.3±1.88
P value	> 0.07	<0.05

Assessment of Tofacitinib

Tofacitinib 5mg/twice daily and Tofacitinib 10mg/twice daily was administered by 45%, 55% of the total population respectively. By assessing the C-reactive protein (CRP) levels in both groups by statistical analysis, Tofacitinib 10mg/twice daily was found to decrease CRP levels than Tofacitinib 5mg/twice daily.

Table 4: Comparison of CRP between Tofacitinib 5mg/twice daily and 10mg/twice daily

TOFACITINIB		
	5mg/twice daily	**10mg/week**
Number of patients	9	11
Initial		
Mean	11.5±3.78	11±3.8
After 3 months		
Mean	9±3.19	9.3±3.04
P value	< 0.05	< 0.05

Assessment of Safety in Methotrexate Group

Safety of the drug was assessed by analyzing side effects associated with the treatment and it was found that Nausea, gastrointestinal disturbances, hypertension, abdominal pain, drowsiness, hair loss, stomach pain, headache and diarrhoea were associated with the treatment of Methotrexate. Majority of the subjects was having nausea and hypertension as side effects in Methotrexate group.

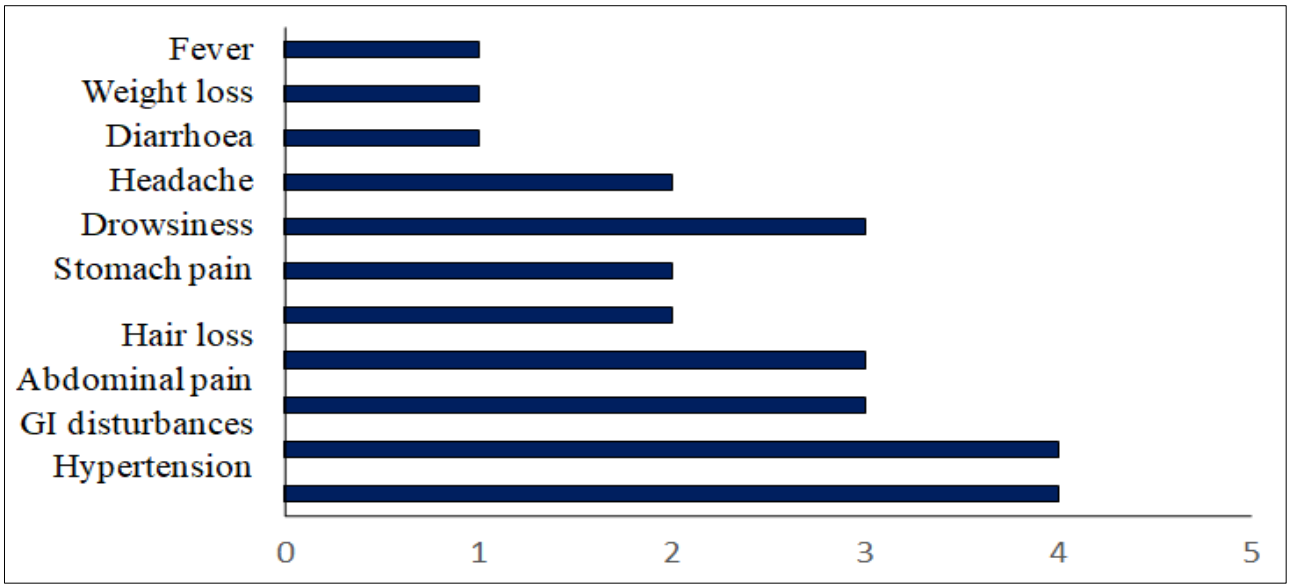


Fig-3: List of side effects observed in the Methotrexate group

Assessment of Safety in the Tofacitinib Group

Safety of the drug was assessed by analysing side effects associated with the treatment and it was found that Hair loss, skin rash, Diarrhoea, Infection, Nasopharyngitis, Constipation, Abdominal pain, wheezing, weight loss were associated with the treatment of Tofacitinib. The majority of the subjects were having hair loss as a side effect in the Tofacitinib group.

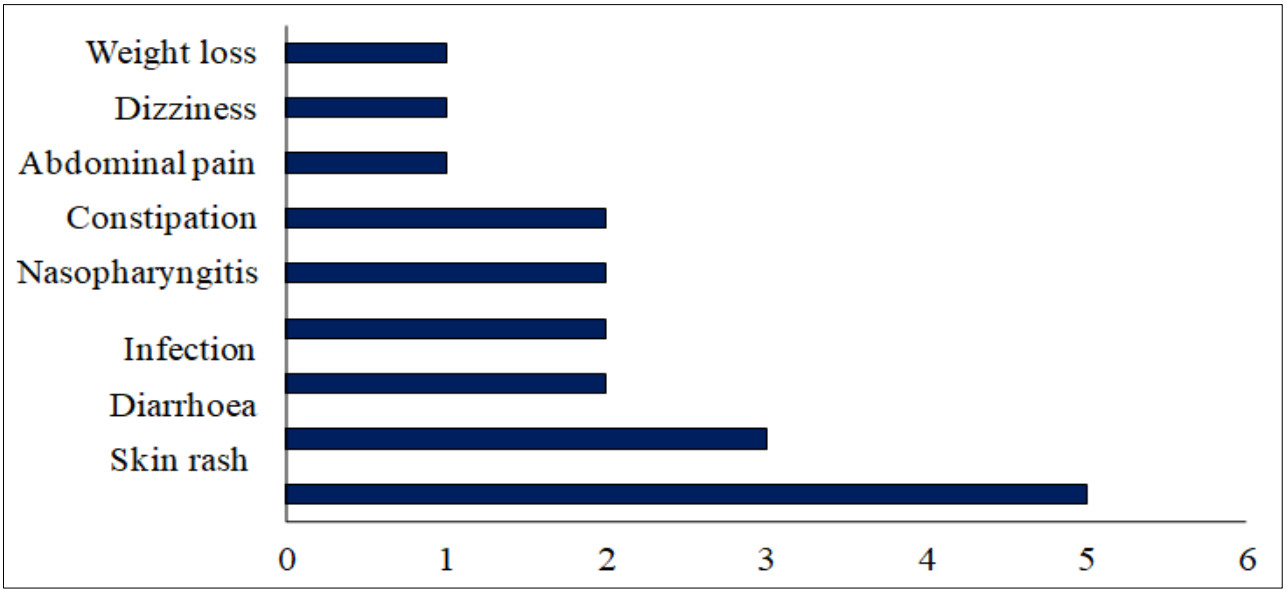


Fig-4: List of side effects observed in Tofacitinib group

Health-Related Quality of Life Assessment in the Methotrexate Group

Average of PCS and MCS in MTX group

The total average of four domains, each under PCS and MCS was found to be 44.12 and 68.75 for PCS and MCS respectively. The overall average of both PCS and MCS was 56.43.

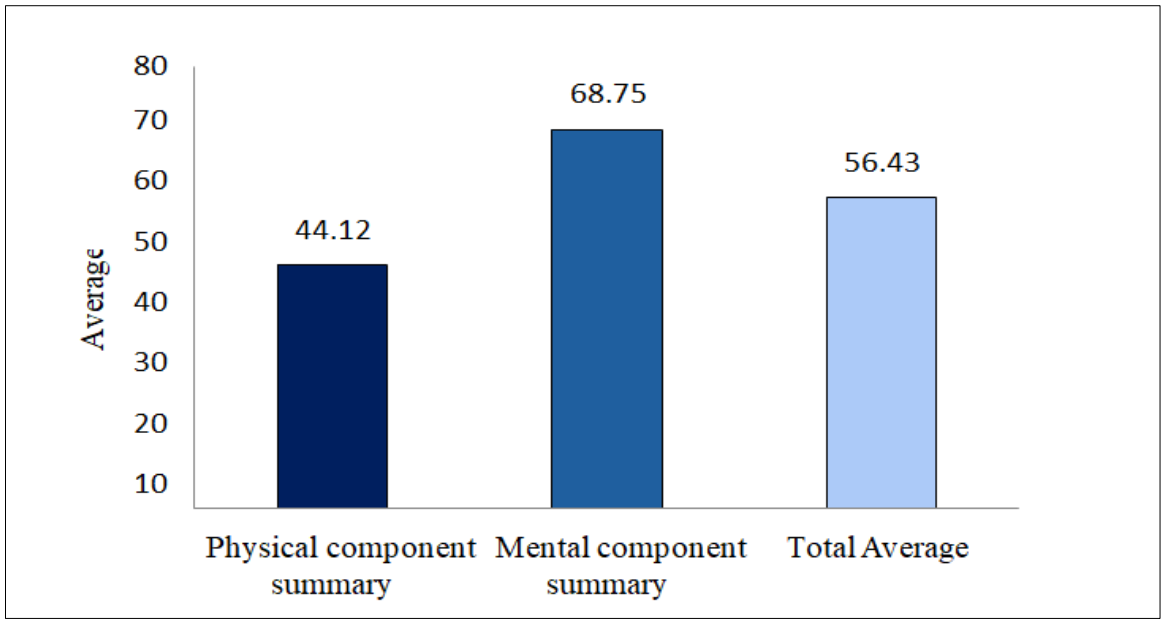


Fig-5: Physical and mental component summary of MTX group

Health Related Quality of Life Assessment in Tofacitinib Group

Average of PCS and MCS in Tofacitinib group

The total average of four domains, each under PCS and MCS was found to be 52.34 and 71 for PCS and MCS respectively. The overall average of both PCS and MCS was 61.68

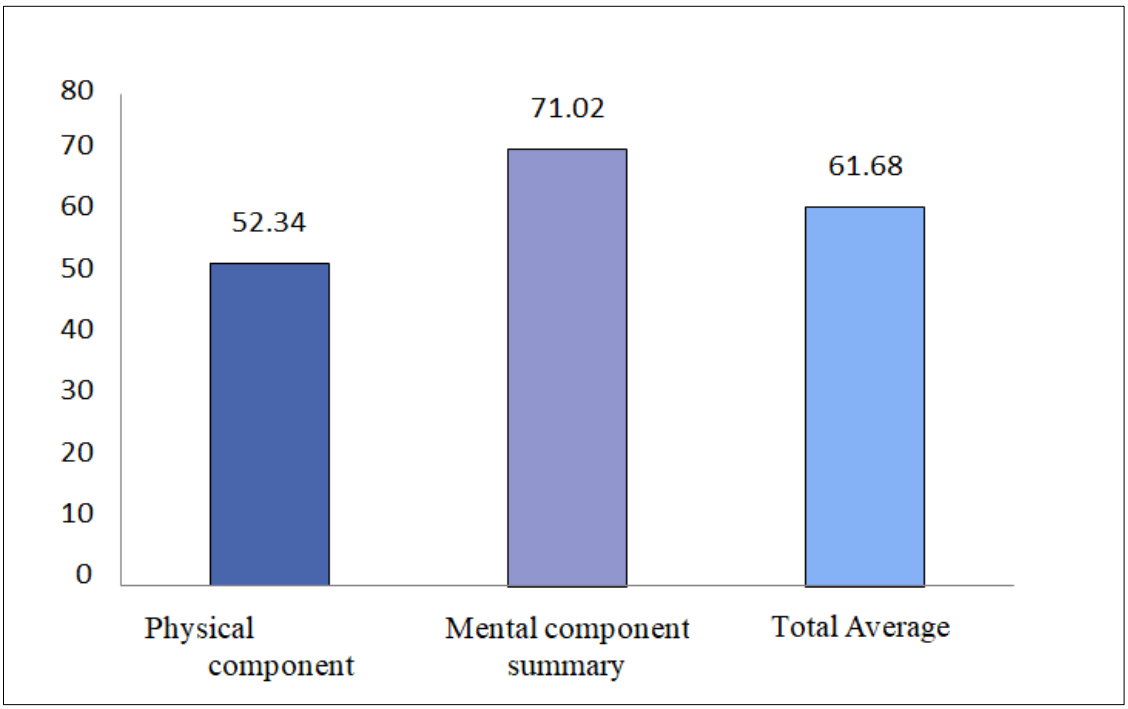


Fig-6: Physical and mental component summary of Tofacitinib group

Comparison of HRQOL in Methotrexate and Tofacitinib Group

On comparing the QOL score in both Methotrexate and Tofacitinib groups, it was found that the subjects belonging to the Tofacitinib group had the highest overall score average ie. 61.68 when compared to the overall score average of Methotexate group ie. 56.43. So the QOL of subjects in Tofacitinib group was much better than Methotrexate group.

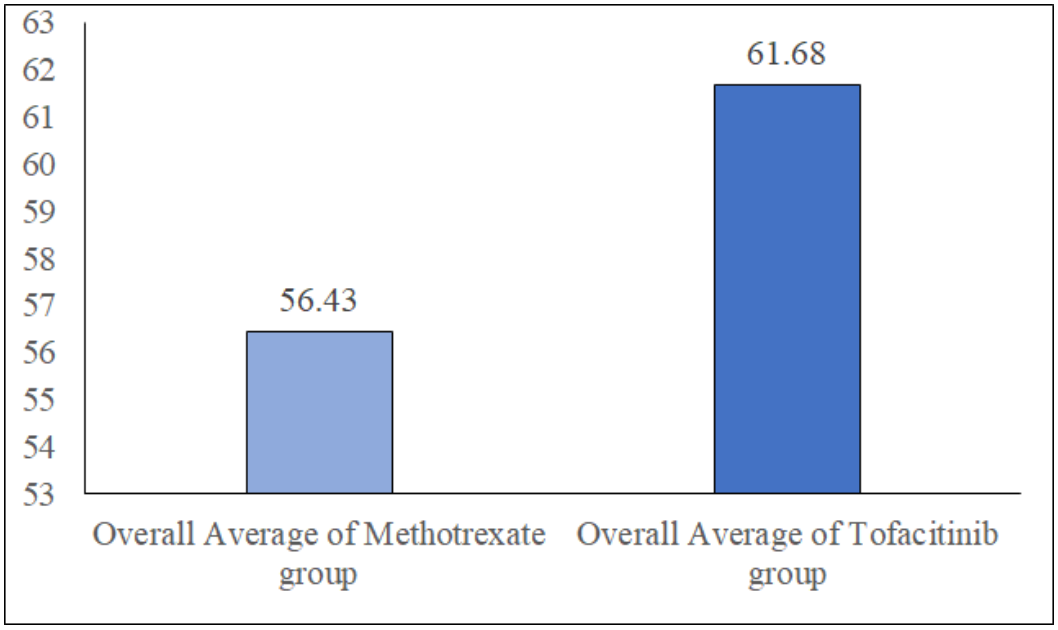


Fig-7: Comaparative Health Assessment Questionnaire – Disease Index For

Methotrexate and Tofacitinib Group

Comparing the effectiveness of both drugs obtained in the HAQ-DI scale revealed that 60% of the population in the Tofacitinib group could perform the eight categories such as dressing. Arising, eating. Walking, hygiene, reach, grip and activity without any difficulty while only 45% of the population on MTX could perform without any difficulty, and 27.5 % of the Tofacitinib group had some difficulty although 35% in the MTX group whereas, 12.5% in Tofacitinib and 20% in MTX had much difficulty. According to HAQ-DI, Tofacitinib had better score than MTX group.

Table 5: Comparison of HAQ-DI between Methotrexate and Tofacitinib group

Parameters	Methotrexate	Tofacitinib
Without any difficulty	45%	60%
With some difficulty	35%	27.5%
With much difficulty	20%	12.5%

DISCUSSUION

The study was a 3 month long observational study performed in selected orthopedic clinics in T. Dasarahalli, Bengaluru district. Based on the inclusion and exclusion criteria, a total of 40 samples were enrolled. The individuals were evenly divided between the two drug groups, with 20 subjects receiving Methotrexate and 20 subjects receiving Tofacitinib. The mean age of all participants irrespective of their drug groups was 52 and the mean age of participants in Methotrexate group was 49 whereas the mean age of participants in Tofacitinib group was 55. Most of the subjects in the study were women and their mean age was 51 and the mean age of men was 54. In this study. It was found that 90% of the subjects were women which is similar to the mean age of participants in the study conducted by Durán J *et al*., and only 10% of subjects were men.

This study conducted in subjects with Rheumatoid Arthritis, compared the treatment with Methotrexate and Tofacitinib with regard to their safety and effectiveness, which was similar to the study conducted by Eun Bong Lee *et al*., The effectiveness of the drugs in this study was assessed based on the reduction of C-reactive protein levels to less than or equal to 6.0mg/L. Both Methotrexate and Tofacitinib administration resulted in persistent reduction of C-reactive protein levels in subjects.

In this study we found that patients receiving Methotrexate 2.5mg/week (30% population) had better reduction in C-reactive protein levels compared to Methotrexate 10mg/week (70% population). This result was attained by performing statistical analysis (paired t-test) and by comparing the obtained mean values of C-reactive protein (initial and after 3months) of both Methotrexate 2.5mg/week ($p = >0.05$) and Methotrexate 10mg/week ($p = <0.05$). Our study had limitation with respect to time period as well as study population owing to the variation in drug dose comparison. And we observed that a higher proportion of patients were receiving Tofacitinib 10mg/twice daily (55% population) and it was found to be more effective than in patients receiving 5mg/twice daily (45% population). Similar to Methotrexate, the result was obtained by comparing mean values of C-reactive protein (initial and after 3months) for both Tofacitinib 10mg/twice daily ($p = <0.05$) and Tofacitinib 5mg/twice daily ($p = <0.05$), a

randomized trial was conducted by Kremer Joel *et al*., where the dose of Tofacitinib was 5mg/twice daily and 10mg/twice daily to evaluate the safety and efficacy of the drug. Comparison of the effectiveness of both Methotrexate and Tofacitinib in the study revealed that Tofacitinib had better effectiveness as it reduced C-reactive protein better than Methotrexate in three months, the result was similar to the study conducted by Eun Bong Lee *et al*., It was obtained from the comparison of mean values of C-reactive protein of Methotrexate and Tofacitinib groups which was found to be 9.78±2 and 9.16±3 respectively. The safety of these drugs were also assessed in our study by analyzing side effects observed during the treatment and the most common side effects observed in the Methotrexate group were nausea (20%) and hypertension (20%), while 15% of the population had abdominal pain, Gi disturbances, drowsiness, a study conducted by Gilani ATS *et al*., found GI disturbance to be the most common adverse effects of Methotrexate. Whereas in the case of Tofacitinib, 25% of the population had experienced hair loss, and 15% had experienced skin rashes. However, the results can not be concluded due to the lack of information on co-morbidities and intake of other drugs, which could have influenced in the observed side effects.

In our study for clinical scoring, we used HAQ-DI to assess the Disability and Functional status of subjects taking Methotrexate and Tofacitinib. HAQ-DI was found to be significant in both drugs by performing statistical analysis. In the Methotrexate group, the average scores of, without any difficulty, with some difficulty, and with much difficulty in DI scale was 10.75±7.8, 6.25±5.5 and 3.1±3.2 respectively which was found statistically significant at $a = 0.05$ ($p=0.05$). For The Tofacitinib group, the average scores of, without any difficulty, with some difficulty, with much difficulty in the Disease Index scale were11.8±6.7, 5.6±4.7 and 2.5±2 respectively which were found statistically significant at $a = 0.05$ ($p=0.003$). Without any difficulty taken as a parameter in the study showed 92% correlation between both drugs.

The HRQOL was assessed using the SF-36 questionnaire, according to the results of the study the average of physical functioning, role limitation due to physical health, pain and general health (physical components) in the study population stood at 60%, 25%, 45% and 46% respectively whereas social functioning, role limitation due to emotional problems, energy and emotional well-being (mental components) stood at 63%, 86.6%,53% and 72%respectively for Methotrexate group, while it was 72.7%, 25%, 62.6%, 49% for physical components and 70.6%, 88.8%, 53.8% and 70.8% for mental components respectively for Tofacitinib group. Among both the groups role limitation due to physical health had lower score as some of the patients found it difficult to do perform day to day activities as it limited them to other activities and took them extra effort or they would shorten the duration of work due to physical condition. Diana Rosa Goncalves *et al.*, conducted a similar study where the HRQOL life was assessed among the Portugal population, and physical component summary had lower values than Mental health status was not affected as well.

By comparing HRQOL score for both Methotrexate and Tofacitinib groups it was found that there was no significant difference between the overall average of physical component summary and mental component summary in both groups, the results from our study were contrary to a study conducted by Birrell FN *et al*., physical and emotional role showed no association with activity measures. In this study, the average PCS and MCS scores of methotrexate was found to be 44 and 68.7 indicating an average HRQOL as 56.4. Similarly the average score of PCS and MCS in Tofacitinib group was found to be 52 and 71 and an average HRQOL as 61.6.

CONCLUSION

The long-term, chronic, and progressive nature of Rheumatoid Arthritis raises serious health concerns as it results in severe joint deformity and functional disability.

The study aimed to compare and assess the safety and effectiveness of Methotrexate and Tofacitinib in Rheumatoid Arthritis patients. In this study using the HAQ-DI questionnaire, Tofacitinib was found to be better than Methotrexate. But the study could not conclude on the drugs' safety profile due to a lack of information on co-morbidities and intake of other drugs, which could have resulted in the observed side effects.

Health-Related Quality of Life has gained importance as an outcome measure in recent studies. The results of the current study indicate that the quality of life of Rheumatoid arthritis patients was significantly low and the most affected domain in the majority of the patients was role limitation due to physical health. Mental health conditions were not much affected in our study when compared to physical health. The study also found those in the Tofacitinib group to have higher Health-Related Quality of Life compared to patients on the Methotrexate group.

These results suggest that Rheumatoid arthritis can be effectively managed with the drug Tofacitinib than Methotrexate. With the help of the findings from our study, a better choice of treatment option can be provided by the physicians to aid in better Quality of life of patients diagnosed with Rheumatoid Arthritis.

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