EFFECTIVENESS OF METHOTREXATE AND SALFASALAZINE ALONE VERSUS METHOTREXATE AND SULPHASALAZINE COMBINATION IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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Abstract:

Background: *Rheumatoid arthritis is a chronic, autoimmune, inflammatory disorder of unknown aetiology that is characterized by symmetric synovitis and the propensity to cause joint destruction, disability and premature death. Disease-modifying anti-rheumatic drugs (DMARDs) slow the natural course of the disease, reduce joint damage and pain, and retard loss of function and disability. Disease modifying agents should be started as early as possible. A number of studies demonstrating the effectiveness of combinations of DMARDs in early RA.*

Methods: *This is a comparative descriptive type of study was conducted in the Department of Medicine, Rangpur Medical College and Hospital, Rangpur & Medicine Specialists Chambers, Rangpur, over a period of 2 (two) years from July 2010 to June 2012 on newly diagnosed RA patients on the basis of ACR criteria. The 30 patients were divided into 3 groups. Group I got MTX, Group II got SSZ and Group III got MTX & SSZ. Purposive consecutive sampling method was employed. The objective of the study was to evaluate the outcome of patients of rheumatoid arthritis treated with MTX or SSZ alone versus MTX and SSZ in combination. The primary outcome measure was change in DAS28.*

Results: *The mean DAS 28 score baseline was found 7.23±0.44 in group I, 7.29±0.39 in group II and 7.86±0.41 in group III. The mean DAS 28 score end of the study was 4.24±0.39 in group I, 4.85±0.54 in group II and 3.08±0.36 in group III. The difference was statistically significant (P<0.001) among the three groups. There is no toxicity found in any group. Regarding side effects, the difference was not statistically significant (P>0.05) among the three groups.*

Conclusion : *This study suggests that the mean changes in the DAS28 score significantly lower in those who received combination therapy compared with those who received either MTX or SSZ alone during one year follow up.*

Key words*: Rheumatoid Arthritis(RA), Methotrexate, Sulfasalazine, DAS 28*

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Introduction:

Rheumatoid arthritis is a chronic, autoimmune, inflammatory disorder of unknown aetiology that is characterized by symmetric synovitis and the propensity to cause joint destruction, disability and premature death[1].Optimal treatment in early disease may provide a window of opportunity leading to improved outcome[2].Disease-modifying anti-rheumatic drugs (DMARDs) slow the natural course of the disease, reduce joint damage and pain, and retard loss of function and disability[3].Disease modifying agents should be started as early as possible.

Current guidelines advise early and sustained use of disease-modifying anti-rheumatic drugs (DMARDs) of which methotrexate (MTX) and sulfasalazine (SSZ) are the most frequently used[4].Both drugs are effective, have an acceptable toxicity and their cost

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is low. MTX and SSZ are used as monotherapy and in combination[5]. Although their mechanism of action remains unclear, several reports suggest that these drugs may differ in their effects on circulating cytokines and cytokine production[6].

Two studies using the combination of drugs used in this study[7]. In the first, a controlled open step-up study in 40 patients "resistant" to SSZ, the combination was significantly better than MTX alone. In the second[8], the individual drugs were compared with the combination in a parallel design from the outset. A modest trend favoring the combination of SSZ and MTX was seen, with comparable results from the two individual drugs. Nausea was documented as an adverse event more often in the combination group.

In general, a combination of two drugs may result in effects that are: multiplicative if one drug promotes the action of the other, additive if both effects add to each other, or sub-addative if the two drugs act in competition. These theoretical interactions are often not well studied when using combinations of DMARDs in real daily practice. Since the combination of MTX and SSZ is frequently used in the therapy for RA and has been tested in several clinical trials, we chose these drugs for the present study.

As the significant number of persons are affected by RA and most of the cases diagnose at the latter part of the course of the disease and initiation of the treatment with DMARDs also start at the latter part of the course of the disease and as a result disease outcome become worse. This study, can draw a conclusion that the initiation of treatment with DMARDs in the early part of the disease will benefit the patients. Commonly the Physician start treatment of Rheumatoid arthritis with single DMARD and when the response is not adequate with single drug then add another one. This study aims to start two DMARDs in initial part of the disease and also to compare the outcome between the patients using two DMARDs and single DMARD by applying DAS 28 score.

Methods:

All cases of RA in patients from July 2010 to June 2012, who were admitted in Rangpur Medical College Hospital and Medicine Specialists Chamber, Rangpur were included in this 24-month 3 arm clinical trial. This study of three groups. Group-I got MTX, Group-II got SSZ & Group-III got MTX+SSZ.

Selection criteria for the patients consists of: Patients of Rheumatoid arthritis as diagnosed by ACR criteria, patients of rheumatoid arthritis in active stage as defined by disease activity score (das28) ^{3} 3.2, patients with RA not yet getting dmards, patients with RA not yet getting steroid, age of onset of symptoms at or above 17 years. Exclusion criteria are : known sulphonamide allergy, pre-existing pulmonary fibrosis, significant renal disease (creatinine> 150mmol/dl), liver disease (ALT>80IU/L), known or planned pregnancy.According to inclusion and exclusion criteria the study subjects were selected. Evaluation of the patients included thorough history taking, meticulous physical examination and relevant investigations. Tables and charts were then made to summarize the various data of interest. The trial was done with all GCD (Good Clinical Practice) criteria. Randomization was done with block and equal distribution was ensured. The clinical trial was acceptance by the institutional ethical review committee.

Statistical analysis:

All data generated was statistically analyzed using the computer based statistical package for the social science (SPSS) in 16.0 version of windows. Levels of significance were calculated at a confidence interval of 95% ($P<0.05$). Comparison among the groups was done by using Chi-square test & Anova test. Comparison within the group at different follow up was done by using paired t-test. Intention to treat analysis and per protocol analysis was done to show efficacy.

Results:

Table-I

Age distribution of the study group of population (n=30)

Age (years)	Group I (n=10)		Group II (n=10)		Group III (n=10)	
	n	%	n	%	n	%
20-30	4	40.0	2	20.0	3	30.0
31-40	4	40.0	5	50.0	2	20.0
41-50	1	10.0	1	10.0	3	30.0
>50	1	10.0	2	20.0	2	20.0
Mean ± SD	35.0±11.07		42.0±11.83		40.6±12.37	

Group I= MTX
Group II= SSZ
Group III= MTX+ SSZ

A total of 30 patients were included in this study and they were divided into three sub groups. The mean age was found 35.0±11.07 years in group I, 42.0±11.83 years in group II and 40.6±12.37 years in group III.

Table-II

Sex distribution of the study group of population (n=30)

Sex	Group I (n=10)		Group II (n=10)		Group III (n=10)	
	n	%	n	%	n	%
Male	5	50.0	3	30.0	4	40.0
Female	5	50.0	7	70.0	6	60.0

Group I= MTX
Group II= SSZ
Group III= MTX+ SSZ

The above table shows the sex distribution of the study patients. Male was found 5(50.0%) in group I, 3(30.0%) in group II and 4(40.0%) in group III. Female was found 5(50.0%), 7(70.0%) and 6(60.0%) in group I, group II and group III respectively.

Table-III

Occupational distribution of the study group of population (n=30).

Occupation status	Group I (n=10)		Group II (n=10)		Group III (n=10)	
	n	%	n	%	n	%
Service	2	20.0	1	10.0	2	20.0
Labourer	2	20.0	0	0.0	0	0.0
Business	2	20.0	2	20.0	2	20.0
Housewife	4	40.0	7	70.0	6	60.0
Unemployed	0	0.0	0	0.0	0	0.0
Others	0	0.0	0	0.0	2	20.0

Group I= MTX
Group II= SSZ
Group III= MTX+ SSZ

Regarding the occupation status, housewife was more frequent among the three groups, which was 4(40.0%) in group I, 7(70.0%) in group II and 6(60.0%) in group III.

The mean ESR was found 87.4±28.07 mm in 1st hour in group I, 80.3±24.26 mm in 1st hour in group II and 89.5±17.71 mm in 1st hour in group III. The mean CRP was found 34.2±15.5, 31.8±14.98 and 31.8±14.98 in group I, group II and group III respectively. The mean difference was not statistically significant (P>0.05) among the three groups by ANOVA test.

Regarding the rheumatoid factor, negative rheumatoid factor was found 2(20.0%) in group I, 2(20.0%) in group II and 2(20.0%) in group III. Low positive rheumatoid factor was found 3(30.0%) in group I, 2(20.0%) in group II and 3(30.0%) in group III. High positive rheumatoid factor was found 5(50.0%) in group I, 6(60.0%) in group II and 5(50.0%) in group III. The difference was not statistically significant (P>0.05) among the three groups in chi square test.

Table-IV

Distribution of the study group of population according to ESR and CRP (n=30).

	Group I (n=10) Mean ± SD	Group II (n=10) Mean ± SD	Group III (n=10) Mean ± SD	P value
ESR (mm in 1st hour)	87.4±28.07	80.3±24.26	89.5±17.71	0.666^{ns}
CRP (mg/dl)	34.2±15.5	31.8±14.98	31.8±14.98	0.920^{ns}

Group I= MTX
Group II= SSZ
Group III= MTX+ SSZ
ns=not significant
P value reached from ANOVA test.

Table-V

Distribution of the study group of population according to rheumatoid factor (n=30).

Rheumatoid factor (IU/mL)	Group I(n=10)		Group II(n=10)		Group III(n=10)		*P* value
	N	%	n	%	n	%	
Negative (≤19)	2	20.0	2	20.0	2	20.0	0.9845^{ns}
Low Positive (20-59)	3	30.0	2	20.0	3	30.0	
High Positive (≥60)	5	50.0	6	60.0	5	50.0	

Group I= MTX
Group II= SSZ
Group III= MTX+ SSZ
ns=not significant
P value reached from chi square test.

Table-VI

Distribution of the study group of population according to anti-CCP (n=30).

Anti citrullinated protein antibody (U/mL)	Group I(n=10)		Group II(n=10)		Group III(n=10)		*P* value
	n	%	n	%	n	%	
Negative (0-5)	5	50.0	2	20.0	3	30.0	0.699 ns
Low Positive (6-15)	1	10.0	2	20.0	2	20.0	
High Positive (>15)	4	40.0	6	60.0	5	50.0	

ns=not significant
P value reached from chi square test.

Positive anti citrullinated protein antibody, low positive was found 1(10.0%) in group I, 2(20.0%) in group II and 2(20.0%) in group III. High positive was found 4(40.0%) in group I, 6(60.0%) in group II and 5(50.0%) in group III. The difference was not statistically significant (P>0.05) among the three groups in chi square test.

Regarding the tender joint count status, the mean tender joint count baseline was found 22.4±5.95 in group I, 21.0±3.16 in group II and 21.0±3.16 in group III. The mean tender joint count at 3 month follow up was 15.9±2.99 in group I, 16.8±2.8 in group II and 14.3±2.3 in group III. The mean tender joint count at 6 month follow up was found 12.2±3.5, 14.1±2.9 and 9.0±1.7 in group I, group II and group III respectively. The mean tender joint count at 12 month follow up of the study was, 2.9±1.86 in group I, 5.0±2.43 in group II and 3.0±1.2 in group III. The mean tender joint count difference at 6 month follow up of the study were statistically significant (p<0.001) in ANOVA test, other were not statistically significant (p>0.05).

Within the group between baseline with follow up at 3 month all groups were statistically significant (p<0.05) in paired t-test.

Within the group between baseline with follow up at 6 month, all groups were statistically significant (p<0.05) in paired t-test.

Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant (p<0.05) in paired t-test.

Table-VII

Distribution of the study group of population according to tender joint count at different follow up (n=30)

Tender joint count	Group I(n=10)	Group II(n=10)	Group III(n=10)	*aP* value
	Mean±SD	Mean±SD	Mean±SD	
Baseline	22.4±5.95	21.0±3.16	21.0±3.16	0.307ns
Follow up at 3 month	15.9±2.99	16.8±2.8	14.3±2.3	0154ns
bP value	**0.003s**	**0.001s**	**0.001s**	
Follow up at 6 month	12.2±3.5	14.1±2.9	9±1.7	0.001s
bP value	**0.002s**	**0.001s**	**0.008s**	
Follow up at 12 month	2.9±1.86	5.0±2.43	3±1.2	0.227ns
bP value	*0.001s*	*0.001s*	*0.001s*	

s=significant; ns=not significant
aP value reached from ANOVA test.
bP value reached from paired t-test.

Table-VIII

Distribution of the study group of population according to swelling joint count at different follow up (n=30).

Swelling joint count	Group I(n=10) Mean±SD	Group II(n=10) Mean±SD	Group III(n=10) Mean±SD	[a]*P* value
Baseline	24.6±6.19	24.2±4.26	24±3.65	0.961[ns]
Follow up at 3 month	14.1±2.9	14.2±2.8	12.7±2.5	0.058[ns]
[b]P value	0.001[s]	0.001[s]	0.001[s]	
Follow up at 6 month	13.5±4.3	14.1±3.7	12.5±2.4	0.126[ns]
[b]P value	0.001[s]	0.001[s]	0.001[s]	
Follow up at 12 month	3.5±1.9	4.46±2.3	2.6±1.2	0.215[ns]
[b]P value	*0.001[s]*	*0.001[s]*	*0.001[s]*	

s=significant; ns=not significant
[a]P value reached from ANOVA test.
[b]P value reached from Paired t-test.

Regarding the swelling joint count status, the mean swelling joint count baseline was found 24.6±6.19 in group I, 24.2±4.26 in group II and 24±3.65 in group III. The mean swelling joint count at 3 month follow up was 14.1±2.9 in group I, 14.2±2.8 in group II and 12.7±2.5 in group III. The mean swelling joint count at 6 month follow up was found 13.5±4.3, 14.1±3.7 and 12.5±2.4 in group I, group II and group III respectively. The mean swelling joint count at theend of 12 month of study was, 3.5±1.9 in group I, 4.46±2.3 in group II and 2.6±1.2 in group III. Not statistically significant (p>0.05) difference were found among the three groups by ANOVA test.

Within the group between baseline with follow up at 3 months all groups were statistically significant (p<0.05) by paired t-test.

Within the group between baseline with follow up at 6 months, months all groups were statistically significant (p<0.05) by paired t-test.

Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant (p<0.05) by paired t-test.

Table-IX

Distribution of the patients according to ESR at different follow up (n=30).

ESR	Group I(n=10) Mean±SD	Group II(n=10) Mean±SD	Group III(n=10) Mean±SD	[a]*P* value
Baseline	87.4±28.07	80.3±24.26	89.5±17.71	0.666[ns]
Follow up at 3 month	75.8±14.7	76.4±14.7	67.2±15.3	0.576[ns]
[b]***P value***	***0.232[ns]***	***0.459[ns]***	***0.018[s]***	
Follow up at 6 month	65.9±13.0	68.5±15.3	53.8±12.4	0.368[ns]
[b]*P value*	*0.036[s]*	*0.041[s]*	*0.001[s]*	
Follow up at 12 month	29.7±7.32	42.2±13.4	24.7±10.7	0.003[s]
[b]*P value*	*0.001[s]*	*0.001[s]*	*0.001[s]*	

s=significant, ns=not significant
[a]P value reached from ANOVA test.
[b] P value reached from paired t- test

Regarding the ESR status, the mean ESR baseline was found 87.4±28.07 in group I, 80.3±24.26 in group II and 89.5±17.71 in group III. The mean ESR at 3 month follow up was 75.8±14.7 in group I, 76.4±14.7 in group II and 67.2±15.3 in group III. The mean ESR at 6 month follow up was found 65.9±13.0, 68.5±15.3 and 53.8±12.4 in group I, group II and group III respectively. The mean ESR at the end of 12 month of the study was, 29.7±7.32 in group I, 42.2±13.4 in group II and 24.7±10.7 in group III. The mean ESR difference end of the study was statistically significant ($p<0.001$) but other were not statistically significant ($p>0.05$) in ANOVA test.

Within the group between baseline with follow up at 3 months, statistically significant ($p<0.05$) difference was found in group III but no statistical significant ($p>0.05$) difference were found in group I and group II in paired t-test.

Within the group between baseline with follow up at 6 month, all groups were statistically significant ($p<0.05$) in paired t-test.

Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant ($p<0.05$) in paired t-test.

Regarding the DAS 28 score status, the mean DAS 28 score baseline was found 7.23±0.44 in group I, 7.29±0.39 in group II and 7.86±0.41 in group III. The mean DAS 28 score at 3 month follow up was 6.69±0.48 in group I, 6.93±0.39 in group II and 5.37±0.45 in group III. The mean DAS 28 score at 6 month follow up was found 5.50±0.39, 5.93±0.40 and 4.26±0.36 in group I, group II and group III respectively. The mean DAS 28 score at the end of 12 month of the study was, 4.24±0.39 in group I, 4.85±0.54 in group II and 3.08±0.36 in group III.

The mean DAS 28 score difference among the groups, at 3 month follow up, 6 month follow up and 12 month follow up of the study were statistically significant ($p<0.001$) but baseline was not statistically significant ($p>0.05$) by ANOVA test.

Within the group between baseline with follow up at 3 month, statistically significant ($p<0.05$) difference was found in group III but no statistical significant ($p>0.05$) difference were found in group I and group II by paired t-test.

Within the group between baseline with follow up at 6 month, all groups were statistically significant ($p<0.05$) by paired t-test.

Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant ($p<0.05$) by paired t-test.

Table-X

Distribution of the patients according to DAS 28 score at different follow up (n=30).

DAS 28 score	Group I(n=10) Mean±SD	Group II(n=10) Mean±SD	Group III(n=10) Mean±SD	^{a}P value
Baseline	7.23±0.44	7.29±0.39	7.86±0.41	0.125^{ns}
Follow up at 3 month	6.69±0.48	6.93±0.39	5.37±0.45	0.001^{s}
^{b}P value	0.104^{ns}	0.083^{ns}	0.031^{s}	
Follow up at 6 month	5.50±0.39	5.93±0.40	4.26±0.36	0.001^{s}
^{b}P value	0.001^{s}	0.018^{s}	0.001^{s}	
Follow up at 12 month	4.24±0.39	4.85±0.54	3.08±0.36	0.001^{s}
^{b}P value	*0.001^{s}*	*0.001^{s}*	*0.001^{s}*	

s=significant, ns=not significant

^{a}P value reached from ANOVA test.

^{b}P value reached from paired t-test

Table XI

Distribution of study group according to side-effects of drugs (n=30)

Side effects	Group-I	Group-II	Group-III	P value
GI upsets	2 (20%)	3 (30%)	2 (20%)	0.741^{ns}
Headache	0 (0)	1 (10%)	1 (10%)	0.585^{ns}

Series 1= Group I= MTX
Series 2= Group II= SSZ
Series 3= Group III= MTX+ SSZ
s=significant, ns=not significant

Regarding side effects GI upsets was found 2(20.0%) in group I, 3(30.0%) in group II and 2(20.0%) in group III. Headache was not found in group I, 1(10.0%) in group II and 1(20.0%) in group III. The difference was not statistically significant (P>0.05) among the three groups in chi square test.

Discussion:

This was 3 arm comparative clinical trial (Phase III) carried out with an aim to find out the clinical pattern of presentation of patients of Rheumatoid Arthritis, evaluate the prognosis of the patients treated with MTX alone versus SSZ and MTX+ SSZ combination, compare the efficacy and toxicity of the treatment, compare the adherence to therapy and determine some selective biological, socioeconomic and biochemical variables as well as to evaluate the outcome of patients having rheumatoid arthritis treated with MTX alone versus SSZ and MTX+ SSZ combination.

A total number of 30 consecutive patients having rheumatoid arthritis treated 10 patients with MTX alone versus 10 patients with SSZ and 10 patients with MTX+ SSZ combination in the Department of Medicine unit, Rangpur Medical College Hospital (RMCH), Rangpur and Medicine Specialist Chamber during the period of July 2010 to June 2012 were included in this study. Patients with rheumatoid arthritis were treated with MTX alone was considered as group I versus SSZ was considered as group II and MTX+ SSZ combination was group III and they were followed up up to the end of the study. The present study findings were discussed and compared with previously published relevant studies.

In this current study it was observed that the mean age was found 35.0±11.07 years in group I, 42.0±11.83 years in group II and 40.6±12.37 years in group III, which were not statistically significant (P>0.05) among three groups. Majority of the patients having rheumatoid arthritis were in 4th decade and above in all three groups. Similarly, Shashikumar et al. (2010) showed the mean age of their study patients were 48.24±11.44 years in group I and 49.33±11.38 years in group II. On the other hand, higher mean age in patients having rheumatoid arthritis, which were 50.9 years, 52.5 years and 48.9 years in group I, group II and group II respectively. Similarly, Barrera et al. (1995) showed mean age was 52.5±13.6 years in group I and 58.9±10.6 years in group II. They have stated that the higher age range maybe due to increased life expectancy in their study patients.

In this present study it was observed that male was found 50.0% in group I, 30.0% in group II and 40.0% in group III. Female was found 50.0%, 70.0% and 60.0% in group I, group II and group III respectively. The difference was not statistically significant (P>0.05) regarding the sex distribution among the three groups of the study patients. Male to female ratio was 1:1.5 in the whole study patients, which indicated that rheumatoid arthritis was more common in female subjects. This gender relationship is equivalent with other authors who also found similar findings, because as is well known that this disease encompasses more women than men ,where the authors showed 78.0%, 84.0% and 76.0% were female in group I, group II and group III respectively.

In this study it was observed that the mean ESR was found 87.4±28.07 mm/hour in group I, 80.3±24.26 mm/hour in group II and 89.5±17.71 mm/hour in group III. The mean CRP was found 34.2±15.5, 31.8±14.98 and 31.8±14.98 in group I, group II and group III respectively. The mean ESR and CRP were not statistically significant (P>0.05) among the three groups.

Regarding the rheumatoid factor, negative rheumatoid factor was found 2(20.0%) in group I, 2(20.0%) in group II and 2(20.0%) in group III. Low positive rheumatoid factor was found 3(30.0%) in group I, 2(20.0%) in group II and 3(30.0%) in group III. High positive rheumatoid factor was found 5(50.0%) in group I, 6(60.0%) in group II and 5(50.0%) in group III. O'Dell et al. (2002) positive 88.0% in patients treated with MTX and HCO, 88.0% in patients treated with MTX & SSZ and 89.0% in patients treated with MTX, HCQ, SSZ, which are closely resembled with the current study.

Positive anti citrullinated protein antibody, low positive was found 1(10.0%) in group I, 2(20.0%) in group II and 2(20.0%) in group III. High positive was found 4(40.0%) in group I, 6(60.0%) in group II and 5(50.0%) in group III. The difference was not statistically significant (P>0.05) among the three groups in chi square test.

Regarding the tender joint count status, in this present series it was observed that, the mean tender

joint count baseline was found 22.4±5.95 in group I, 21.0±3.16 in group II and 21.0±3.16 in group III. The mean tender joint count at 3 month follow up was 15.9±2.99 in group I, 16.8±2.8 in group II and 14.3±2.3 in group III. The mean tender joint count at 6 month follow up was found 12.2±3.5, 14.1±2.9 and 9.0±1.7 in group I, group II and group III respectively. The mean tender joint count end of the study was, 2.9±1.86 in group I, 5.0±2.43 in group II and 3.0±1.2 in group III. The mean tender joint count status decline in all three groups but at 6 month follow up it was significantly ($p<0.05$) more decline in group III. Within the group between baseline with follow up at 3 month all groups were statistically significant ($p<0.05$) in paired t-test. Within the group between baseline with follow up at 6 month, all groups were statistically significant ($p<0.05$) in paired t-test. Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant ($p<0.05$) in paired t-test.

In this study it was observed that the mean swelling joint count baseline was found 24.6±6.19 in group I, 24.2±4.26 in group II and 24±3.65 in group III. The mean swelling joint count at 3 moths follow up was 14.1±2.9 in group I, 14.2±2.8 in group II and 12.7±2.5 in group III. The mean swelling joint count at 6 months follow up was found 13.5±4.3, 14.1±3.7 and 12.5±2.4 in group I, group II and group III respectively. The mean swelling joint count end of the study was 3.5±1.9 in group I, 4.46±2.3 in group II and 2.6±1.2 in group III. The mean swelling joint count status improved in all three groups but not significantly ($p>0.05$) improved in any follow-up among the three groups. Whereas within the group between baseline with follow up at 3 month all groups were statistically significant ($p<0.05$) by paired t-test. Within the group between baseline with follow up at 6 month, all groups were statistically significant ($p<0.05$) by paired t-test. Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant ($p<0.05$) by paired t-test. In a study patients who had achieved vast improvements mentioned are the results achieved by the hand grip and duration of morning stiffness, but fewer results have been achieved in relation to the swelling of PIP joints[9].

Regarding the ESR status, the mean ESR baseline was found 87.4±28.07 in group I, 80.3±24.26 in group II and 89.5±17.71 in group III. The mean ESR at 3 month follow up was 75.8±14.7 in group I, 76.4±14.7 in group II and 67.2±15.3 in group III. The mean ESR at 6 month follow up was found 65.9±13.0, 68.5±15.3 and 53.8±12.4 in group I, group II and group III respectively. The mean ESR at the end of 12 month of study was 29.7±7.32 in group I, 42.2±13.4 in group II and 24.7±10.7 in group III. The mean ESR decreased in all three groups but at end of the study follow up were significantly ($p<0.05$) more decrease in group III, whereas others were not significant ($p>0.05$). Within the group between baseline with follow up at 3 month, statistically significant ($p<0.05$) difference was found in group III but no statistical significant ($p>0.05$) difference were found in group I and group II in paired t-test. Within the group between baseline with follow up at 6 month, all groups were statistically significant ($p<0.05$) in paired t-test. Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant ($p<0.05$) in paired t-test.

Regarding the DAS 28 score status in this series it was observed that the mean DAS 28 score baseline was found 7.23±0.44 in group I, 7.29±0.39 in group II and 7.86±0.41 in group III. The mean DAS 28 score at 3 month follow up was 6.69±0.48 in group I, 6.93±0.39 in group II and 5.37±0.45 in group III. The mean DAS 28 score at 6 month follow up was found 5.50±0.39, 5.93±0.40 and 4.26±0.36 in group I, group II and group III respectively. The mean DAS 28 at score at the end of 12 month of the study was 4.24±0.39 in group I, 4.85±0.54 in group II and 3.08±0.36 in group III. The mean DAS 28 score status improved significantly ($p<0.05$) at all follow up among three groups. Within the group between baseline with follow up at 3 month, statistically significant ($p<0.05$) difference was found in group III but no statistical significant ($p>0.05$) difference were found in group I and group II by paired t-test. Within the group between baseline with follow up at 6 month, all groups were statistically significant ($p<0.05$) by paired t-test. Within the group between baseline with follow up at 12 month of the study, all groups were statistically significant ($p<0.05$) by paired t-test. The primary outcome was measured the mean change in DAS observed[10]. As can be expected, the mean DAS changes were lower in SSZ than in DMARD-naive patients. This is in accordance with current evidence that treatment should be initiated in the early stages of RA in order to reduce disease activity most effectively: to achieve and sustain clinical remission[11].

Besides the efficacy evaluation, it was noticed that the safety profile of the combination group in our study seems acceptable without any synergistic effect. Minor side effects like, GI upsets was found 2(20.0%) in group I, 3(30.0%) in group II and 2(20.0%) in group III. Headache was not found in group I, 1(10.0%) in group II and 1(20.0%) in group III. The difference was not statistically significant ($P>0.05$) among the three groups in chi square test. Similar, findings were also documented[12].

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Conclusion:

This study suggests that the mean changes in the DAS28 score significantly lower in those who received combination therapy compared with those who received either MTX or SSZ alone during one year follow up. Combination showed no drug toxicity or had not been stopped in any patients due to side effects. The combination of MTX and SSZ, is relatively inexpensive. Combination of MTX & SSZ proved more effective than monotherapy in patients of Rheumatoid arthritis.

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