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Research Article

CHOLINE MAGNESIUM TRISALICYLATE VS NAPROXEN IN THE SYMPTOMATIC TREATMENT OF RHEUMATOID ARTHRITIS: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Aim: This study was aimed to evaluate the comparative efficacy and tolerability of Choline Magnesium Trisalicyliate (CMT) versus Naproxen (NA) in the symptomatic treatment of Rheumatoid arthritis (RA) in Indian subjects.

Methods:This was a 12 week, phase III, multicentric, open label, prospective, comparative study, conducted in the outpatient setup. Sixty eligible subjects, who gave written informed consent, were treated with either CMT 2000 mg/day for four weeks followed by 3000 mg/day for further eight weeks or NA 500 mg/day for four weeks followed by 1000 mg/day for further eight weeks, as per the allocation procedure.

DAS 28 (Disease activity score in 28 joints), which was the primary efficacy parameter and the global evaluation of efficacy and tolerability, which were the secondary efficacy parameter were assessed [by the investigator (IGA) and patient (PGA)] during each visit. The global assessment of gastric tolerability was done using the Global Overall Symptom scale at each follow up visit.

Results: Both drugs showed similar efficacy in terms of reduction in tender and swollen joint counts, severity of pain and improvement in general health. Reductions in DAS 28 score during the treatment period in both groups indicated a symptomatic improvement. Improvement in IGA and PGA scores from baseline were noted in both groups, but this was statistically insignificant. The safety profile in both drugs did not differ significantly throughout the study.

Conclusion:We conclude that CMT has an efficacy and safety profile comparable to that of Naproxen and could be considered as an alternative choice in the symptomatic treatment of RA.

Keywords: cmt, naproxen*, RA,* DAS 28, Gastric tolerability, IGA, PGA

INTRODUCTION

Rheumatoid arthritis (RA), a progressive autoimmune disease of unknown etiology, causes joint destruction, deformity, disability and premature death[1]. The prevalence rate of RA is 1%, with women affected three to five times as often as men. The prevalence of RA in Indian adults is similar to that reported from developed countries[2].

Management of RA requires a holistic approach including medical, social, and emotional support for the individual. Prognosis is judged by the response to the treatment, positive response indicating a better prognosis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as salicylates are the first line of treatment for RA in the symptomatic management. However, renal and hepatic toxicity, especially in elderly and high risk subjects limits its use in these individuals.

Studies have shown that non-acetylated salicylates such as Choline magnesium trisalicylate (CMT) are less nephrotoxic [3,4] and CMT has better safety profile than Acetyl Salicylic Acid (ASA)[5,6].

CMT is in use for the symptomatic management of rheumatoid arthritis, osteoarthritis and other arthritides.

This study was carried out to evaluate comparative efficacy and tolerability of CMT versus a commonly prescribed NSAID i.e., Naproxen (NA) in the treatment of rheumatoid arthritis (RA) in Indian subjects.

METHODS

Patients

Sixty (60) eligible subjects of both genders [Male = 13 (21.67%), Female = 47 (78.33%)] above 18 years with rheumatoid arthritis for more than six months (Diagnosed on basis of ACR Criteria for Rheumatoid arthritis), who met the selection criteria and gave written informed consent, were screened and enrolled in the trial from five centers in India.

Pregnant and lactating females, subjects with history of hypersensitivity to aspirin and /or other NSAIDs, active peptic ulcer disease, or recent gastrointestinal bleeding or perforation, Crohn's disease or ulcerative colitis, severe insufficiency of the cardiac function (NYHA class III / IV) , subjects recovering from major surgery, chronic hepatic disease or abnormal liver function test (LFT) and abnormal renal functions, and subjects with pre-existing hepatic porphyria were excluded from the study. Subjects with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis/those at high risk of bleeding, and those on naproxen or immunosuppressant therapy were also excluded; however, those on Methotrexate therapy were allowed to participate in the study.

Study Design

This was a 12 week, phase III, multicentric, open label, prospective comparative study, conducted in outpatient setup from April 2009 to September 2009.

Methods

This study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki. Study documents such as the protocol, case report form, statement of informed consent etc., were approved by Drugs Controller General of India and the Institutional Ethics committees prior to study initiation. Written informed consent was obtained from each subject prior to entry into the study.

Information on demographic characteristics like age, gender, height, body weight, blood pressure (BP), heart rate (HR), co-existing illness, concomitant medications with their dose and duration were recorded.

Eligible patients were randomized using a simple randomization list to Group-A -CMT and Group-B –Naproxen respectively.

Subjects in Group-A were treated with CMT 2000mg/day for 4 weeks followed by 3000mg/day for further 8 weeks. Those in Group-B received Naproxen 500mg/day for initial 4 weeks followed by 1000mg/day for further 8 weeks.

Enrolled subjects were followed up at the following visits -Visit 1 (Week 0), Visit 2 (Week 2), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12).

Efficacy assessment

During each visit, subjects were assessed using DAS28 (Disease activity score in 28 joint) [7], a validated and reliable self-administered questionnaire to assess the degree of severity of the disease and the response of the drug throughout the study period.

At baseline and at the end of the study, vital signs, physical examination, assessment of joint function using DAS 28 score, X-ray of the affected joint and safety laboratory investigations were performed. At subsequent visits, physical examination and assessment of joint function using DAS 28 index was carried out and adverse events if any were recorded.

The secondary efficacy parameter was assessed by the investigator using the Investigator Global Assessment (IGA) scale and by the patients using Patient's Global Assessment (PGA) Scale during each follow up visit.

The gastric tolerability of the drug was assessed by the investigator using seven point Global Overall Symptom (GOS) scale during each follow up visit.

Safety Assessment

During each visit, disease severity, occurrence of adverse events, and gastric tolerability were assessed and recorded. Number of acid neutralizing drugs dispensed and returned was also recorded during each visit.

Safety laboratory investigations, IGA and PGA assessment were performed at the end of study visit.

Drug accountability was also maintained to note treatment compliance. Adverse events i.e., their nature, intensity, outcome and causal relationship to study medication were also recorded.

Safety evaluations specified for the final visit were performed for those completed the study and those who withdrew prior to week 12.

Statistics

All demographic characteristics including age, height, body weight, BP and HR were compared between two groups by using two sample't' test.

Two sample independent 't' test was used to compare the difference in reduction of DAS scores between two treatment groups. Paired 't' test was used to compare the safety parameters in the baseline and at the end of study. Two sample Wilcoxon rank-sum test was used to compare the difference in reduction of pain intensity scores between two treatment groups.

IGA and PGA were compared in both groups by using two sample Wilcoxon rank– um test. Adverse events were coded using MedDRA version 13.1 and were summarized using frequency counts.

Change in biochemical parameters from baseline to end of study was evaluated using paired t-test in both groups.

The frequency distributions of subjects for all the biochemical assessment variables were categorized as "Below Normal", "Normal" and "Above Normal".Adverse events in between the two groups were compared using 2 × 2 Fisher's exact test.

Incidence of Adverse Events [including serious adverse event (SAE)] was summarized using frequency counts.

Concomitant Medication was categorized by generic name and summarized using frequency count.

Compliance was assessed at each visit and was computed as number of tablets taken/number of tablets expected to be taken. The average of all visits of a particular subject was taken as his/her overall compliance.

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed using STATA version 10.1 for Windows (Stata Corp, College Station, TX).

RESULTS

Demography

Sixty eligible subjects from five centres in India, who gave written informed consent were enrolled in the trial. Of these, data for 56 patients were analysed for efficacy. Four patients whose post baseline data for efficacy parameters were not available, hence were excluded from analysis.

Both groups were similar statistically in terms of age, height, weight, BP and HR.

Of 51 patients who completed the study, 24 were in CMT group and 27 were in Naproxen group. Six in CMT group and three in Naproxen group dropped out from the study at different stages due to various reasons. Details are provided in Fig 1.

EFFICACY

Efficacy analysis

Both drugs were effective in reducing the number of tender & swollen joints, pain intensity and in improving general health at all follow up visits beginning from baseline; however, there was no statistically significant difference at any of the visits between both treatment groups was observed (Figure 2, 3, 4 and 5).

DAS 28 Score

There was no statistically significant difference in DAS 28 score between the two groups at baseline.

There was a significant improvement ($p<0.000$) in DAS 28 score at each of the visits compared to baseline in both CMT and Naproxen groups indicating that both drugs were effective. However, there was no statistically significant difference in DAS 28 score at each of the visits between the two study groups during the study period (Table 1).

Table 1: Comparison of Mean DAS 28 score at each visit

Visits	CMT				Naproxen				p value
	No. of Patients	Mean	SD	C I	No. of patients	Mean	SD	C I	(between groups)
Week 0	28	5.54	0.86	5.21, 5.87	29	5.41	0.87	5.08, 5.74	0.57
Week 2	27	4.93	1.19	4.46, 5.40	29	4.77	1.03	4.38, 5.16	0.60
Week 4	24	4.28	0.95	3.88, 4.68	28	4.31	0.79	4.01, 4.62	0.87
Week 8	24	3.68	1.26	3.14, 4.21	27	3.53	0.99	3.14, 3.92	0.64
Week 12	24	2.98	1.09	2.52, 3.44	27	2.92	0.92	2.56, 3.29	0.84

There was a statistically significant reduction in mean of DAS 28 score during the treatment period in both treatment groups; however, there was no statistically significant difference was noted between the groups.

Investigator's Global Assessment and Patient's Global Assessment (IGA and PGA).

There was a statistically significant agreement ($p < 0.00$) between the Investigator and the patients assessment regarding efficacy at all visits in both groups. Figure 6 and 7 shows the distribution of IGA and PGA at the end of the study.

Both drugs were well tolerated in nearly 50% of the patients as per the assessments by the investigator and the patient. There was a statistically significant agreement ($p < 0.00$, kappa statistics was used) between the investigator and the patient regarding the tolerability to treatment at all visits in both groups.

Figure 1: Study flow chart

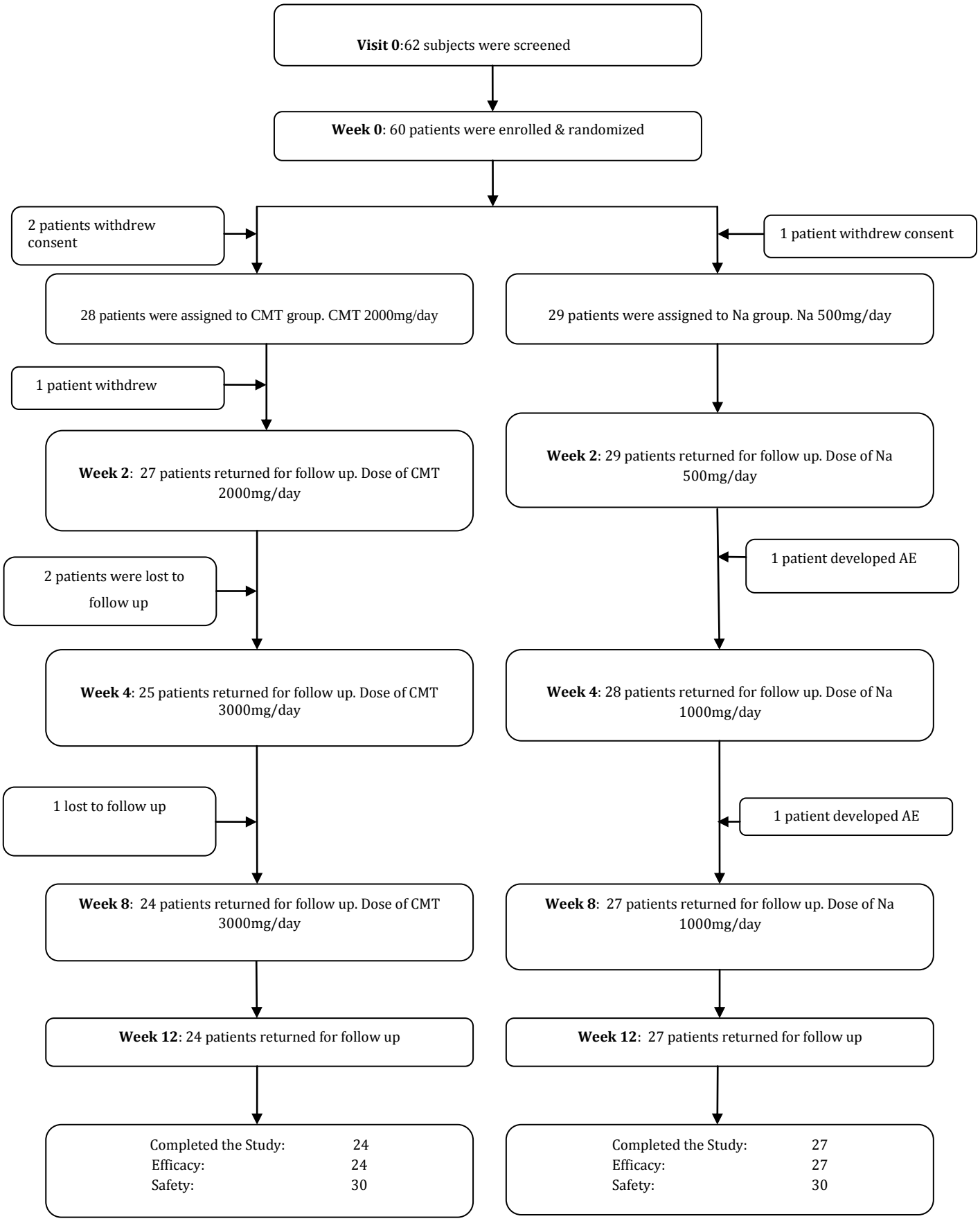

Table 2: Details of AE due to which subjects withdrew consent

Study medication	AE	Severity	Relation to study medication	Outcome
CMT	Gastritis	Mild	Probable	Resolved
CMT	Itching- skin	Mild	Not related	Unchanged
NA	Worsening of RA	Mild	Probable	Resolved

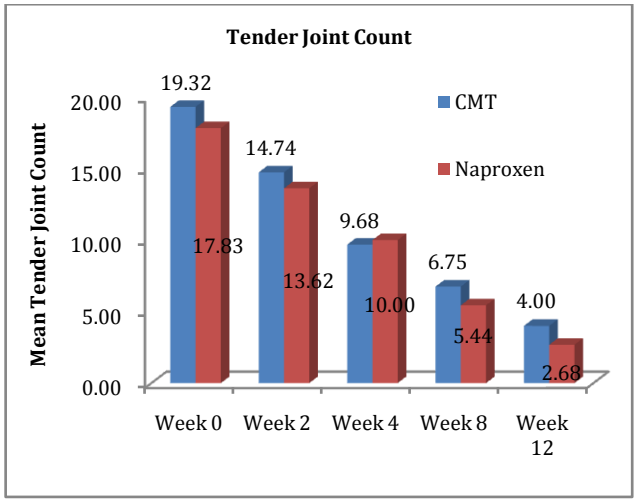

Figure 2: Comparison of Tender joint counts between CMT and Naproxen

There was a statistically significant reduction in the number of tender joints at all visits compared to baseline in both treatment groups; however, there was no significant difference was noted between both groups.

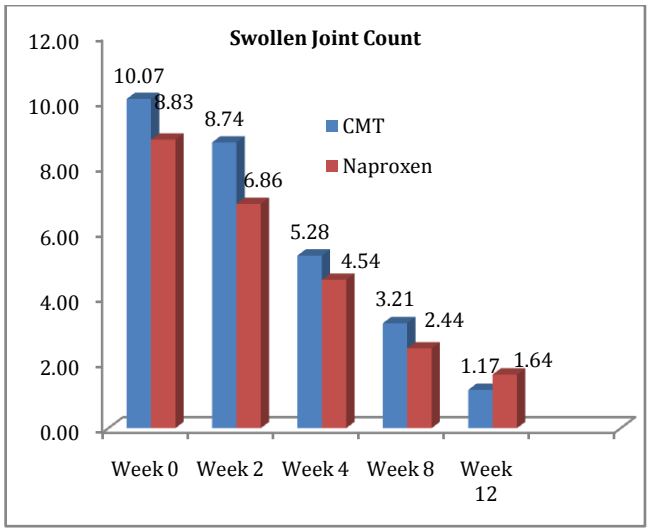

Figure 3: Comparison of Swollen Joint Count between CMT and Naproxen.

There was a statistically significant reduction in the number of swollen joints at all visits compared to baseline in both treatment groups; however, there was no significant difference was noted between both groups.

Safety Assessments

Both drugs exhibited similar safety profiles. One patient in the CMT group, who developed an AE, withdrew the consent after enrollment but before week 2 and the detail of which were not available. One patient in the Naproxen group developed dyspnoea and was diagnosed to have pulmonary fibrosis, unrelated to study medication.

There were no SAEs during the study in either the CMT or the Naproxen group.

There was no significant change in laboratory parameters studied except in two patients, who were receiving Methotrexate 7.5mg twice a week in addition to CMT. They developed significantly elevated AST and ALT levels by the end of study, which returned to normal after two weeks of discontinuing the study drug.

Two patients in CMT group and one patient from Naproxen group withdrew from the study due to adverse events (Table 2). Overall compliance was very good with all subjects identified as taking the prescribed study medication with compliance greater than 90%.

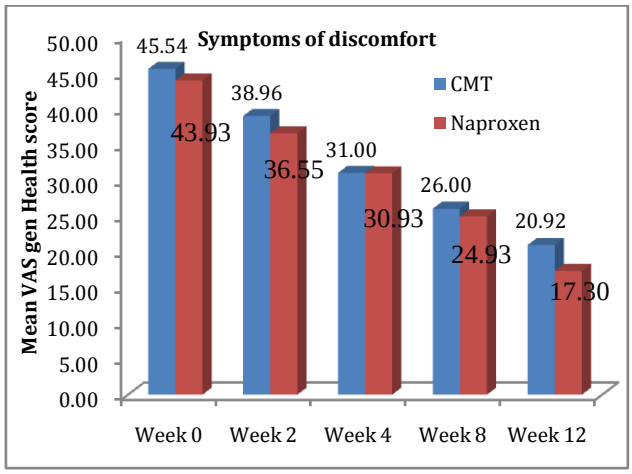

Figure 4: Comparison of General Health

There was a statistically significant improvement in the general health as measured by VAS general health score, at all visits compared to baseline in both treatment groups; however, there was no significant difference was noted between both groups.

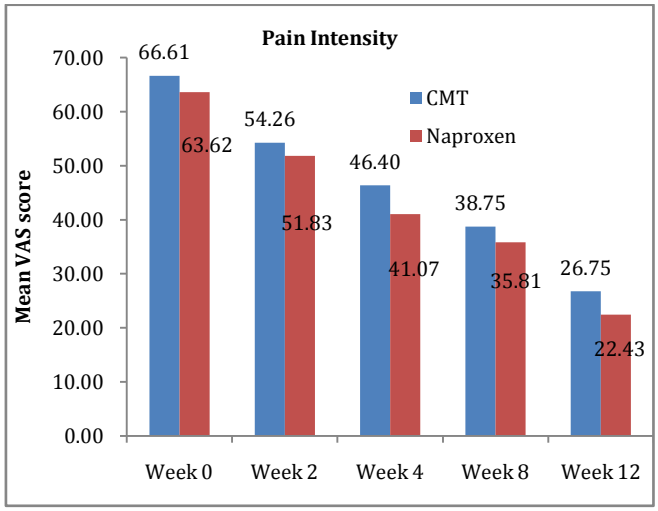

Figure 5: Comparison of Response of Pain to CMT and Naproxen.

There was a statistically significant reduction in the pain intensity measured by VAS score at all visits compared to baseline in both treatment groups; however, there was no significant difference was noted between both groups.

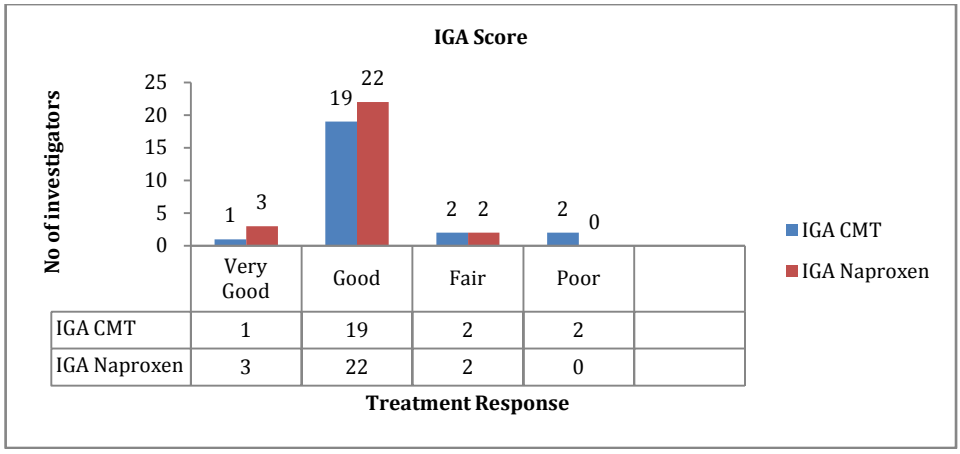

Figure 6: Comparison of IGA scores for CMT and Naproxen

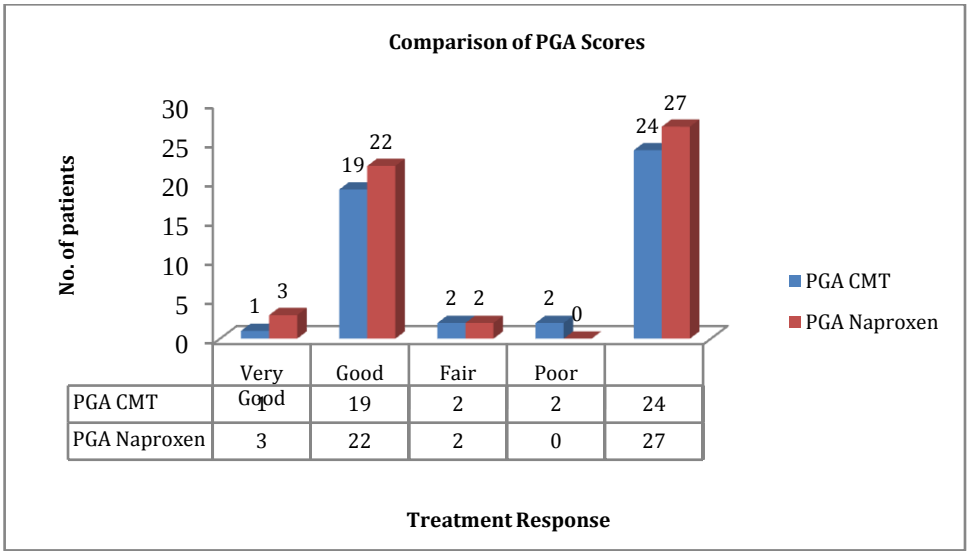

Figure 7: Comparison of PGA scores CMT and Naproxen

DISCUSSION

Despite the advances in the treatment of rheumatoid arthritis, NSAIDs still remain cornerstone in the symptomatic treatment of RA, even in patients on effective DMARD (Disease Modifying Anti Rheumatic Drug) regimes. The present study demonstrates that anti-inflammatory and analgesic activity of CMT is comparable to the conventional NSAID Naproxen, in symptomatic management of RA.

Earlier studies [8] have shown that patients with RA respond to NSAIDs which reduces the inflammation and pain associated with RA, thereby improving the functional ability of treated patients. Our study demonstrated that theses two NSAIDs used in this study are effective in reducing the inflammation and other symptoms associated with RA confirming the results of the previous studies. However, there was no statistically significant difference between the two groups. Earlier study also has shown substantial efficacy of CMT [9] similar to that with Naproxen and the results of the present study confirm the same. This supports the use of CMT in the symptomatic management of RA.

The most common drug-related adverse event observed with CMT and Naproxen was gastritis of mild severity. Being NSAIDs these gastrointestinal side effects are expected. [9] There was no statistically significant difference in number of patients with adverse events at any of the visits in both groups in our study. Those subjects who had elevated AST and ALT levels also received Methotrexate and concomitant use of Methotrexate could have resulted in the elevation of enzymes.. Hepatic toxicity resulting in significant elevation of liver enzymes has been reported with the chronic use of Methotrexate.[10]

There were consistencies in the therapeutic response as indicated by the statistically significant agreement between the investigator and patients.

It was observed that there was a statistically significant agreement ($p < 0.000$) between the Investigator and the patient regarding efficacy and tolerability at all visits in both groups.

Salicylates have been used for more than a century and have a well documented history of general tolerability. Greater reduction in swollen joint count was achieved with CMT [9] with less adverse events. [11, 12]

The results of our study show that CMT has an efficacy comparable to Naproxen with a similar safety profile. This study concludes a beneficial role for the use of CMT in the symptomatic management of RA.

CONCLUSION

As RA is a progressive disease of the joints associated with pain and inflammation, analgesics are the important agents in the symptomatic treatment of the condition. Though many NSAIDs are available in the market, they are associated with adverse events, which limit its long term use. There has been a continuous search for a novel agent in the management of RA. CMT has been proved to be safe and efficacious in comparison with ASA and other NSAIDs like Ibuprofen and has shown comparable efficacy and safety with Naproxen.

This trial has shown that CMT has an efficacy comparable with Naproxen in the symptomatic treatment of RA and it is plausible to

state that it can be used as first line treatment for RA. If symptomatic disease control is ineffective with CMT or it is not well tolerated, it may be replaced by other alternate approaches. However, minimum effective dose of CMT should be used to minimize the adverse effects. We recommend clinical trials in a large population to confirm these findings.

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