

# A Comparative Study of Efficacy and Tolerability of Fixed-Dose Combination of Etoricoxib and Thiocolchicoside versus Thiocolchicoside alone in Patients with Painful Muscle Spasms

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Nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants are widely prescribed for the highly prevalent painful muscle spasms. But there appears to be lack of published clinical study comparing the efficacy and tolerability with the intended study drugs. To compare the efficacy and tolerability of the fixed-dose combination (FDC) of Etoricoxib-Thiocolchicoside versus Thiocolchicoside alone in patients with painful muscle spasms. A prospective, open-label, randomized comparative study of 100 eligible outpatients with painful muscle spasms of either gender aged between 18 to 65 years were randomly assigned to receive oral medications b.i.d for 7 days of either FDC of Etoricoxib (60mg)-Thiocolchicoside(4mg) (GROUP-1) or Thiocolchicoside (4mg) (GROUP-2) alone. The primary efficacy endpoint assessed by the percentage reduction in the intensity of pain utilizing a 10 cm Visual Analogue Scale (VAS) on movement and at rest was significant in both groups ( $p < 0.0001$ ) but more pronounced with GROUP-1 than GROUP-2 ( $p < 0.05$ ) on day 7 compared to day 1. The secondary efficacy endpoint assessed by patient and clinician using Global Assessment of Response to Therapy (GART) on a 5 point scale showed significantly larger number of patients with excellent to a very good response for GROUP-1 compared to GROUP-2. Though both the groups were well tolerated, the GART score for tolerability was more excellent in GROUP-2 than GROUP-1. Any adverse events during the study period was also recorded. The Etoricoxib -Thiocolchicoside combination is more effective with faster pain relief and less tolerable than Thiocolchicoside monotherapy, in treating patients with painful muscle spasms.

**Keywords:** Etoricoxib-Thiocolchicoside; Muscle Spasms; Thiocolchicoside; Visual Analogue Scale.

Muscle spasms occurring in the general population are of varying prevalence depending upon various etiologies.<sup>1</sup> They accompany degenerative or inflammatory diseases affecting the musculoskeletal system.<sup>2</sup> Muscular spasms may occur when there is involuntary and forcible contraction of the muscle and cannot relax, as seen in conditions when it is overused, strained,

fatigued as a result of stress, over exercising or dehydration. Usually it is self-limiting but if it delays, the consequences of it include absenteeism from work, unwarranted hospital and treatment costs and sometimes disablement. Its impact is seen on the society economically and socially.<sup>3</sup> Therefore this condition should be addressed and effectively managed.

By definition, a muscle spasm is a sustained involuntary contraction of a muscle that is usually painful and cannot be relieved completely by voluntary effort.<sup>2</sup> Conditions involving backache, neuralgias, torticollis, lumbosacral strain are associated with painful muscle spasms, which are treated with short-term use of centrally acting muscle relaxants combined with analgesics; but efficacy and tolerability are not impressive.<sup>4</sup>

Skeletal muscle relaxants are a class of drugs belonging to the diverse group, whose utility is seen in conditions involving centrally to reduce the muscle tone by acting at the cerebrospinal axis or to reduce muscular pain or spasms by acting peripherally at the neuromuscular junction or muscle fibre.<sup>5</sup> Having a different mechanism of action, most of them act via their sedative property.

In general, majority of the centrally acting skeletal muscle relaxants used to treat muscle spasms have significant side effects such as sedation, drowsiness, mental confusion, weakness, ataxia, hallucinations, sudden withdrawal symptoms and anticholinergic side effects like dry mouth. Therefore, often the patient shows reduced compliance which leads to inefficacy in managing the painful spasms, resulting in reduced work capacity.<sup>4</sup>

Thiocolchicoside is derived semi-synthetically from colchicine which is extracted from the flower seeds of the species *Gloriosa superba* and *Colchicum autumnale*.<sup>6,7,8</sup> It acts on the inhibitory neurotransmitters, glycine and gamma-aminobutyric acid (GABA)-A receptors, of the central nervous system. It is a muscle relaxant with anti-inflammatory and additive analgesic effects.<sup>9,10,11</sup> It is clinically used from past four decades for the treatment of muscle pain and contractures in patients with orthopaedic, rheumatologic, or musculoskeletal disorders. It is used in various formulations-oral, parenteral, topical via transdermal and in the form of non-greasy topical foams or gels.<sup>11,12</sup> Being well-tolerated, it has the advantage of reduced or no sedative effects, which is a drawback in the use of other muscle relaxants. Its non-sedative property can be explained due to non-interference with nicotinic receptors.<sup>8,13</sup>

Non-steroidal anti-inflammatory drugs are the medications which are routinely used for various

musculoskeletal conditions worldwide. Currently, the selective Cyclooxygenase (COX)-2 inhibitors, a subclass of NSAIDs, have superseded the traditional NSAIDs which inhibit both consecutive COX-1 (responsible for gastrointestinal adverse effects) and inducible COX-2. Though the COX-2 NSAIDs and traditional NSAIDs show no significant difference statistically in the reduction of pain, the former has fewer gastrointestinal complications.<sup>14,15</sup>

Etoricoxib is a newer selective COX-2 inhibitor, having greater COX-2 selectivity compared to its congeners rofecoxib, valdecoxib, or celecoxib with gastroprotection being its advantage over other traditional NSAIDs.<sup>15</sup> Fixed-dose combinations of NSAIDs and skeletal muscle relaxants may cause reduction in pain by acting through two different mechanisms and also the combined skeletal muscle relaxant can reduce the doses of NSAID making them much more favourable.<sup>3,16,17</sup>

Firstly, despite using skeletal muscle relaxants and analgesics for painful muscle spasms, the outcome is less promising and hence there is a need to reduce the social and economic disability by choosing an appropriate pharmacotherapy. Secondly, there are a lot of research done involving NSAIDs and muscle relaxants in FDC's but no published data comparing the FDC's of Etoricoxib and thiocolchicoside with thiocolchicoside monotherapy. Hence this comparative study to evaluate the objectives, efficacy and tolerability of the above two groups of drugs is conducted on the subjects with painful muscle spasms.

## MATERIALS AND METHODS

### Study Design

This prospective comparative study which was randomized and open-label was conducted from December 2018 to May 2019 in the Orthopaedic outpatient department (OPD) of Kempegowda Institute of Medical Sciences, Bangalore. Approval of the study protocol was taken from the Institutional Ethics Committee and as well, obtaining written informed consent from all the study subjects. Registration of the trial was done with Clinical Trial Registry India (CTRI/2018/11/022223).

**Study subjects**

A total of 100 participants who fulfilled the specified inclusion and exclusion criteria were screened and then randomized to receive either of the two treatment protocols.

**Inclusion criteria**

All male and female subjects aged between 18-65yrs presenting to the Orthopaedic OPD with localized, uncomplicated, non-traumatic painful muscle spasm of recent onset (1-30 days) and who are willing to give written informed consent and available for regular follow up and examination were included in the study.

**Exclusion criteria**

Subjects with a history of kidney and liver damage, gastrointestinal bleeding or acid peptic diseases, cardiovascular disease, pregnant and lactating mothers, those allergic to NSAIDs and skeletal muscle relaxants or prior history of hypersensitivity reactions or asthma; those potentially requiring auxiliary treatment; those who were treated with NSAIDs or skeletal muscle relaxants 1 week before the study; those with severe concurrent systemic diseases including bleeding diathesis, on anticoagulant therapy and those with osteoporosis, malignancy, or previous surgical history of lumbar spine were excluded from the study.

**Treatment procedure**

After obtaining the demographic data and relevant medical history from the eligible study subjects, they underwent randomization through simple randomization procedure in the ratio 1:1 divided equally into two treatment groups, GROUP-1 and GROUP-2, each receiving the b.i.d dose of the treatments for 7 days. GROUP-1 (50 subjects) received FDC of Etoricoxib (60mg) with Thiocolchicoside (4mg) and GROUP-2 (50 subjects) received Thiocolchicoside (4mg) alone. Follow up of the study subjects was done for another week to ascertain complete remission of pain and none of them required any rescue medications.

**Efficacy assessments**

The primary efficacy outcome measure was evaluated for the intensity of pain at rest and on movement on day 1 (visit 0, baseline), day 3 (visit 1), and day 7 (visit 2) using a 10 cm Visual analogue scale (VAS) as reported by a patient

where 0 implies no pain and 10 implies unbearable pain.

The secondary efficacy outcome measure included Global Assessment of Response to Therapy (GART). The clinician and the patient independently assessed the efficacy and tolerability at the end of the study (day 7) on a 5 point scale (0-Poor, 1-Fair, 2-Good, 3-Very Good, 4- Excellent).

At each visit the adverse events if any, were recorded.

**Statistical analysis**

A sample size of 100 participants was calculated (50 in each group) based on 90% prevalence of the disease as stated in previous studies, with a 95% confidence interval (CI), 5% type I error, and precision of 0.05.

Results for continuous data were expressed as mean  $\pm$  standard; the discrete data were represented as numbers and percentages. Variables, within the group, were compared with paired t-test. Variables, between the groups, were compared with an independent t-test. Non-parametric data which included Global Assessment of Response to Therapy (GART) was assessed using Mann-Whitney U-test. 95% confidence level ( $p < 0.05$ ) was taken as statistical significance.

**RESULTS**

In our study, 100 subjects were totally enrolled, with 50 in both the groups and all of them finished the study. Figure 1 depicts the flow of study participants. The demographics and the baseline characteristics are compared as in Table 1.

Of the 100 participants, 60% ( $n=60$ ) were female participants and 40% ( $n=40$ ) were male participants ( $p=0.13$ ). There was no statistically significant difference with the gender distribution ( $p > 0.05$ ). The incidence of muscle spasms was found to be more among the age group 35-45years ( $n=28$ , 28%) as shown in the Table 2 and Figure 2. Mean body weight was  $65.15 \pm 4.55$  in GROUP-1 and  $63.11 \pm 5.43$  in GROUP-2. Mean height was  $160.23 \pm 2.45$  in GROUP-1 and  $162.83 \pm 5.67$  in GROUP-2.

**Primary Efficacy endpoint**

Pain scores as assessed by VAS showed a statistically significant reduction ( $p < 0.0001$ ) with

movement and at rest from day 1 to day 7 within the group. Also between GROUP-1 and GROUP-2 there was a statistically significant difference in

the reduction of pain scores ( $p < 0.05$ , 95% CI). The above findings are depicted in Table 3. The corresponding percentage improvement in pain

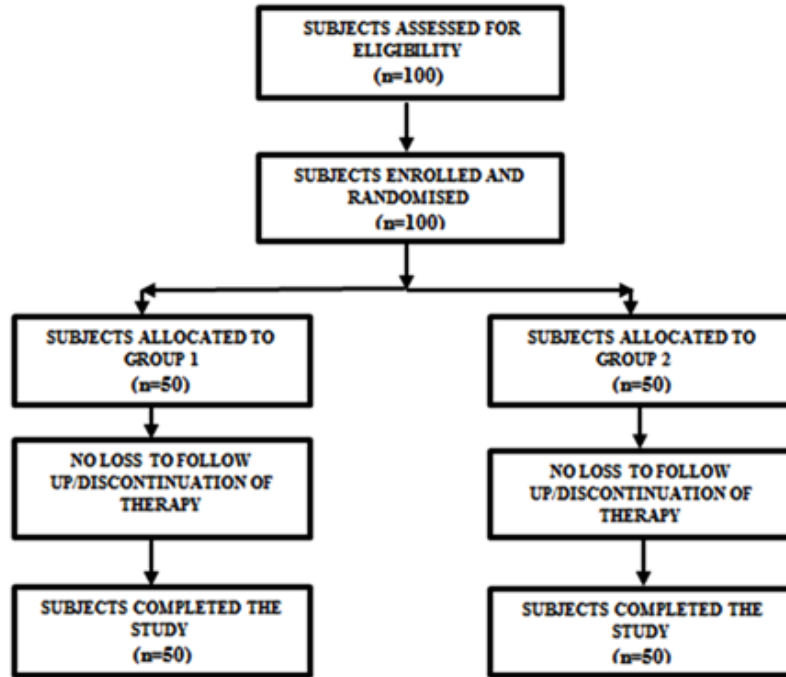


Fig. 1. Study Flowchart

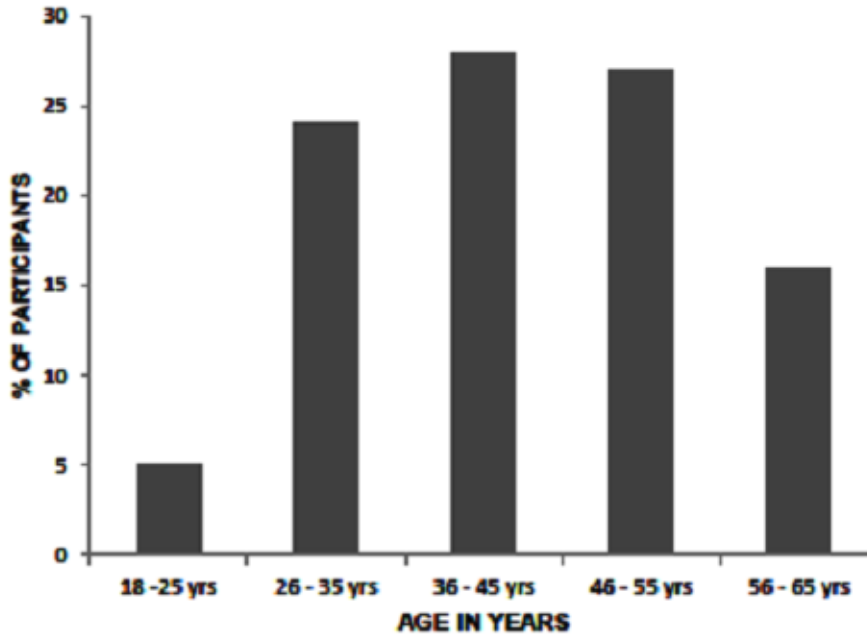


Fig. 2. Distribution of age across the groups

relief from day 1 to day 3 to day 7 with movement and at rest in both the groups is shown in Figure 3a and Figure 3b respectively.

The mean ( $\pm$  SD) VAS score with movement reduced from  $7.02 \pm 1.22$  at baseline

to  $2.28 \pm 1.60$  on day 7 in GROUP-1 and  $7.54 \pm 0.84$  at baseline to  $3.1 \pm 1.29$  on day 7 in GROUP-2. Similarly the mean ( $\pm$  SD) VAS score at rest reduced from  $6.04 \pm 1.59$  at baseline to  $1.26 \pm 1.32$  on day 7 in GROUP-1 and  $6.44 \pm$

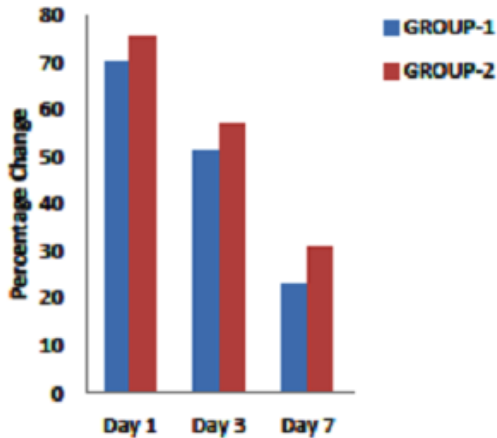


Fig. 3a. Percentage change in the intensity of pain relief with movement in GROUP-1 and GROUP-2 as per VAS

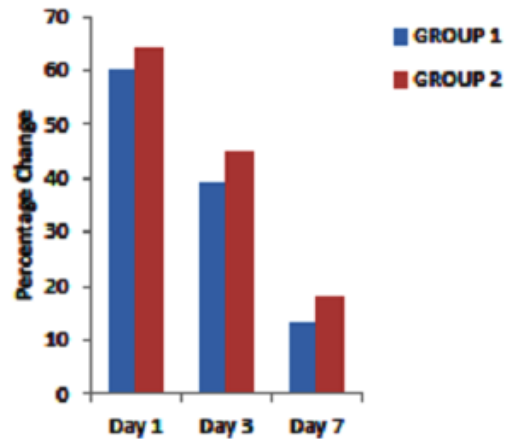


Fig. 3b. Percentage change in the intensity of pain relief at rest in GROUP-1 and GROUP-2 as per VAS



Fig. 4a. Global efficacy assessment by the patients



Fig. 4b. Global efficacy assessment by the clinician



Fig. 5a. Global assessment of tolerability by the patients



Fig. 5b. Global assessment of tolerability by the clinician

0.96 at baseline to  $1.82 \pm 1.22$  at rest on day 7 in GROUP-2. However, the percentage reduction in the pain severity was greater within GROUP-1 than GROUP-2 ( $p < 0.05$ , 95% CI).

#### Secondary efficacy endpoint

The Global efficacy assessment by the patient was rated as excellent to a very good response for GROUP-1 (52%-44%) compared to GROUP-2 (46%-40%) as shown in Figure 4a. The Global efficacy assessment by the clinician was from excellent to very good in GROUP-1 (64%-30%) which was better compared to GROUP-2 (60%-32%) as shown in Figure 4b. The Global tolerability scores as assessed by the patient ranges from excellent to very good in both the groups but were found to be better in GROUP-2 ranging between (84% to 14%) compared to (78% to 10%) in GROUP-1 as shown in Figure 5a. Similarly, the Global tolerability assessment done by the clinician showed a better response ranging between excellent to very good in GROUP-2 (94% to 4%) compared to GROUP-1 (82% to 8%) as shown in Figure 5b.

#### Safety

About 24% ( $n=12$ ) of the subjects had adverse events in GROUP-1 compared to 14%

( $n=7$ ) in GROUP-2 as depicted in Table 4. A total of 19 adverse events were reported. The commonest adverse event was gastritis complained by 7 subjects in GROUP-1 and 2 subjects in GROUP-2. Other adverse events complained in GROUP-1 were nausea ( $n=3$ ), itching ( $n=1$ ), drowsiness ( $n=1$ ). In GROUP-2 the adverse events reported were nausea ( $n=1$ ), dizziness ( $n=1$ ), drowsiness ( $n=2$ ) and dyspepsia ( $n=1$ ). These reported adverse events were possibly associated to the study medications and were of mild to moderate intensity requiring not much intervention or discontinuation of the therapy.

## DISCUSSION

Painful muscle spasms are the most frequently encountered acute problem occurring in all age groups and are also seen in any occupation related to stress. Although it is mild and subsides in due course of time, quick relief and easy healing with minimal adverse effects is desired to comfortably get back to the daily routine in our life.<sup>18</sup> Many therapeutic interventions have been tried for this purpose but remain unsatisfactory.

**Table 1.** Demographic and baseline characteristics

Parameters	Group- 1 (Etoricoxib + Thiocolchicoside) n=50	Group- 2 (Thiocolchicoside Alone) n=50	p Value <sup>a</sup>
Age (yrs)	38.44 ± 11.32*	38.36 ± 10.53*	0.9709
Weight (kgs)	66.8 ± 8.02*	68.12 ± 7.11*	0.3860
Height (cm)	159.74 ± 4.81*	161.43 ± 6.57*	0.1454
Gender (%)	Male	18 (9%)	0.7401
	Female	32 (16%)	0.7805

\*Results are expressed as mean ± standard deviation. <sup>a</sup>Significance (p value) obtained using an unpaired t-test

**Table 2.** Age and gender distribution

Age (Yrs)	Male	Female	Percentage of Participants
18-25	2	3	5%
26-35	7	17	24%
36-45	11	17	28%
46-55	14	13	27%
56-65	6	10	16%
Total	40%	60%	p value = 0.13

Among the commonly prescribed medications worldwide, the traditional NSAIDs, newer selective COX-2 inhibiting NSAIDs, and muscle relaxants form the basis for treating muscle spasms due to their analgesic and anti-inflammatory properties.<sup>14,15</sup>

In this study, the results suggested that though both FDCs of the Etoricoxib with Thiocolchicoside and Thiocolchicoside monotherapy showed similar efficacy;

**Table 3.** Evaluation of primary efficacy endpoint (intensity of pain relief) as per VAS

Intensity of pain	Group-1 Etoricoxib+ Thiocolchicoside <sup>a</sup> (n=50)	Group-2 Thiocolchicoside <sup>a</sup> (n=50)	P-value*	95% CI
Baseline Day 1 Mean± SD	7.02 ± 1.22	7.54 ± 0.84	0.0148	0.1043-0.9357
At Rest	6.04 ± 1.59	6.44 ± 0.96	0.1310	-0.1213-0.9213
Day 3 Mean ± SD	5.08 ± 1.47	5.66 ± 1.12	0.0288	0.0614-1.0986
At Rest	3.94 ± 1.57	4.48 ± 1.16	0.0533	-0.0078-1.0878
Day 7 Mean ± SD	2.28 ± 1.60	3.1 ± 1.29	0.0058	0.2432 – 1.3968
At Rest	1.26 ± 1.32	1.82 ± 1.22	0.0299	0.0556 -1.0644
P-value <sup>δ</sup> (Between day 1 to day 7)	<0.0001	<0.0001		

<sup>a</sup>Results are expressed as mean ± standard deviation(SD)

\*Significance (P value) obtained using an unpaired t-test

<sup>δ</sup>Significance (P value) obtained using a paired t-test

Thiocolchicoside monotherapy had fewer adverse events compared to the FDCs.

In the present study, there was a higher percentage of female participants compared to male participants; though non-significant it is found in accordance with the previous study conducted by Ajya Sah and Rudip Thapa, where female participants were 57% and male participants were 43%.<sup>3</sup> However, in the study conducted by Raut Asawari et al. the male participants (82.5%) were predominant to female participants (17.5%).<sup>19</sup>

The percentage of individuals presenting with painful muscle spasms are more in the age group of 36-45yrs (28%), 46-55yrs (27%) which is similar to the study Ajya Sah and Rudip Thapa<sup>3</sup> and Anil Pareek et al<sup>16</sup> suggesting that it is more common with increasing age (middle and elderly individuals ) due to the stress-related, work-related injuries or due to lack of adequate physical activity.<sup>20</sup> Also, this age group represents the working-age group and, long-term absenteeism from work due to the ailment is not desired.<sup>1,14</sup> Hence an appropriate and effective medication that offers quick and immediate relief has to be proposed.

Though the pain reduction has been seen significantly (p<0.0001) in both the groups, the primary efficacy endpoint which included pain scores has been reduced more in the Etoricoxib and Thiocolchicoside group than the Thiocolchicoside monotherapy group (p<0.05). There has been no study with this combination of drugs, but studies have been made with different combinations of NSAIDs with muscle relaxants. In the Ajya Sah and Anil Pareek studies, the efficacy of aceclofenac plus tizanidine has been better compared to

**Table 4.** Adverse events reported in both the study groups

Adverse Events	Group 1 (n=50)	Group 2 (n=50)
Gastritis	7	2
Nausea	3	1
Itching	1	0
Dizziness	0	1
Drowsiness	1	2
Dyspepsia	0	1
Total	(n=12) 24%	(n=7) 14%

aceclofenac alone.<sup>3,16</sup> In Raut Asawari et al diclofenac and thiocolchicoside reduced more pain than diclofenac alone<sup>19</sup> and in Sachdeva et al Aceclofenac and Thiocolchicoside reduced more pain scores compared to Aceclofenac.<sup>20</sup> This shows the superiority of the FDC's over Thiocolchicoside alone due to their additive effect.

In the secondary efficacy endpoint, the patient and the physician efficacy parameter was better in GROUP 1 compared to GROUP 2 showing the superiority of the combined combination over the single muscle relaxant.<sup>18,21</sup>

But in some cases and some studies, the skeletal muscle relaxants like Tolperisone and Thiocolchicoside used alone have shown better efficacy compared to placebo, and also for tolerability they have an upper hand compared to the NSAIDs.<sup>1,19</sup>

Though both groups are safe with very few adverse effects, in this study, adverse events were more in the combination group and more with Etoricoxib than thiocolchicoside. Etoricoxib has more adverse effects with gastritis hence less tolerable than thiocolchicoside. Unlike other muscle relaxants, Thiocolchicoside has been reported to have less gastrointestinal side effects and was well tolerated.<sup>23</sup> The extension of its pharmacological actions has been shown as the side effect of a centrally acting skeletal muscle relaxant.

The limitations of the study are that the sample size is small and it is an open-label study. This can be addressed by conducting multicenter randomized control study to establish the beneficial effect of the FDC of Etoricoxib and Thiocolchicoside in various other acute pains with muscle spasms with a larger study population.

### CONCLUSION

In the present study for the treatment of painful muscle spasms, the fixed-dose combination of Etoricoxib and Thiocolchicoside has shown better efficacy with faster pain relief compared to Thiocolchicoside alone though it is more tolerable than the combination therapy.

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### Conflicts of Interest

There are no conflicts of interest.

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