Targeting the Therapeutic Need in Musculoskeletal Inflammatory Pain with Thiocolchicoside and Aceclofenac Sustained-Release Combination Therapy

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Abstract

Context: Musculoskeletal pain is usually associated with inflammation and muscular spasm which further contributes to the elevation of pain. Traditionally, nonsteroidal anti-inflammatory drugs (NSAIDs) are employed in the treatment of pain. Literature review reveals that the benefits were more significant in terms of overall symptom reduction, when the patients suffering from musculoskeletal pain were administered the combination of a NSAID & a muscle relaxant. Aims: The present study was undertaken with the aim to assess the efficacy and safety of fixed-dose sustained-release combination of aceclofenac and thiocolchicoside in patients with acute inflammatory conditions associated with muscle spasm. Settings and Design: A multicenter, prospective, open-label, noncomparative clinical study was carried out in 442 patients with clinical diagnosis of inflammation associated with spasm. Subjects and Methods: A fixed-dose combination of aceclofenac (200 mg) and thiocolchicoside (8 mg)-sustained-release capsules was orally administered once daily for 2 weeks. Results: The treatment led to significant pain reduction from the baseline noted with visual analog score at the 1st week itself. After 2 weeks of treatment, the mean pain score declined by 90%, joint tenderness improved in 90% of the patients, and the mean joint mobility scores were near normal in most of the patients. Furthermore, at the end of the treatment, nearly all of the patients were symptom free. No serious adverse events were reported. Conclusions: The current study confirms that fixed-dose combination of aceclofenac and thiocolchicoside in sustained-release form is effective and well tolerated in the treatment of patients with acute musculoskeletal inflammatory conditions.

Keywords: Aceclofenac, muscle relaxant, musculoskeletal pain, nonsteroidal anti-inflammatory drugs, thiocolchicoside

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage that can significantly interfere with the person’s quality of life and overall functioning.[1] It is a very common complaint among all the age groups, and every individual experiences it at least once in a lifetime. Among the clinically relevant pain conditions, pain associated with the musculoskeletal system is most frequent. Musculoskeletal pain is usually associated with inflammation and muscular spasm which is responsible for persistent pain.[2] Chronic musculoskeletal pain is defined using the ICD-11 classification system as “persistent or recurrent pain that arises as part of a disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s).”[3]

Higher incidences of pain are reported in the Indian population in all the age group of people majorly due to occupational exposure and lack of physical activity.[4,6] It is a major health problem and is associated with work absenteeism and inability to perform due to physical unfitness.[7]

The overall goal for musculoskeletal pain management is to improve comfort and restore maximize and preserve function.[8] In general, musculoskeletal pain is managed with

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the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and centrally acting skeletal muscle relaxants. NSAIDs are the most common analgesics used in almost all types of patients suffering from painful musculoskeletal conditions. These drugs can prevent the production of inflammatory mediators involved in producing pain, such as prostaglandins owing to inflammation and cell injury. Centrally acting muscle relaxants are commonly indicated for the treatment of muscular pain or spasms from peripheral musculoskeletal diseases or injury such as low back pain. Muscle relaxants are largely used in combination with other analgesic drugs such as NSAIDs. Combination of these classes of drugs has shown to be effective in improving the tolerability and overall therapeutic outcome.

Aceclofenac is a phenylacetic acid derivative that inhibits the synthesis of the inflammatory cytokines such as interleukin-1β and tumor necrosis factor-alpha and inhibits prostaglandin E2 production. Aceclofenac is indicated for the symptomatic treatment of pain and inflammation in various conditions including acute and chronic pain. Aceclofenac is a long-acting, well-tolerated with lower incidence of side effects and has an established safety profile which provides sustained pain relief by preferentially blocking cyclooxygenase II enzyme.

Thiocolchicoside is a semisynthetic derivative of colchicine, a natural glycoside originated from the flower seeds of Gloriosa superba. It has an affinity for the inhibitory glycine and gamma-aminobutyric acid (GABA)-A receptors, therefore showing muscle relaxant action. As it has GABA-mediated action, thiocolchicoside shows both myorelaxant and analgesic activities. Thiocolchicoside has demonstrated its clinical efficacy and safety in many clinical trials and has also been reported to produce muscle relaxation without any sedative side effects. The relative efficacies of these two drugs, aceclofenac and thiocolchicoside, are, therefore, complimentary for effective relief from inflammation and muscle spasm, ultimately leading to superior analgesic effect.

The elimination half-life of thiocolchicoside is up to 5 h and around 4 h for aceclofenac, creating the need to take these medications twice in a day. In addition, both the drugs can be associated with some kinds of side effects; however, not all the patients may experience it. The beneficial effect can be achieved, along with the enhancement of overall therapeutic outcome, by reducing the number of drug administration as compared to conventional dosing. Sustained-release dosage form is formulated for various reasons, but the important benefit is a reduction in the dosing frequency to once a day which may increase the patient compliance. There will be a small amount of drug released for a long period of time giving prolonged therapeutic efficacy. Furthermore, sustained-release formulation will provide a uniform blood concentration as well as more predictable drug delivery. Hence, a sustained-release formulation of thiocolchicoside and aceclofenac combination could improve patient convenience and provide better patient compliance by considerably lengthening the interval between administrations.

The present study was undertaken to assess the efficacy and safety of fixed-dose sustained-release combination of aceclofenac and thiocolchicoside capsules for the treatment of patients with acute inflammatory conditions associated with muscle spasm.

**Subjects and Methods**

**Design of investigation**

A prospective, open-label, noncomparative, and multicenter study included 442 patients with clinical diagnosis of musculoskeletal inflammation associated with spasm. The postmarketing surveillance study was conducted at >10 different centers (not >50 patients at each center) in India by qualified investigators. Treatment effectiveness was assessed at visit II (day 7) and visit III (day 14). Efficacy evaluation was carried out based on improvement in parameters such as pain intensity, tenderness, joint mobility, and time needed by the patient to be symptom free. Safety assessment was carried out depending upon the occurrence of adverse event (if any) and its severity. At the end of the treatment, global assessment of efficacy and tolerability was confirmed by the physicians and patients.

**Treatment procedure**

Demographic data and relevant medical history were obtained from all patients prior to initiation of therapy. Patients received fixed-dose combination of aceclofenac 200 mg and thiocolchicoside 8 mg sustained-release capsules (Thioceclo SR®) once daily. At each visit, patients were asked to report adverse effects present (if any).

**Inclusion criteria**

Patients of either sex in the age group between 18 and 55 years with painful muscle spasms and contractions associated with cervical and lumbar spondylosis, rheumatoid arthritis, osteoarthritis, blunt superficial trauma, and musculoskeletal low back pain.

**Exclusion criteria**

Hypersensitivity has been reported to any of the ingredients of the formulation. Patients with painful muscle spasms associated with musculoskeletal systems, which need parenteral therapy/surgery/hospitalization for management. Patients were treated with any other oral/parenteral muscle relaxants and analgesics (NSAIDs and opioids) within 1 week prior to the enrollment in the study.

Patients who are suffering from organic neurological disorders and peripheral vascular diseases; patients who are suffering from myasthenia gravis or myopathies with prominent symptom of muscle weakness; patients with severe diseases related to the functioning of cardiac, hepatic, gastrointestinal, renal, pulmonary, and skin; and also pregnant and lactating females were not included in the study.
Criteria for evaluation
The efficacy of the combination therapy was evaluated at day 7 and day 14 after treatment initiation.

The visual analog scale was assessed for evaluating the reduction in the pain intensity at every visit: 0 = no pain, 1–2 = mild pain, 3–4 = moderate pain, 5–6 = severe pain, 7–8 = very severe pain, and 9–10 = worst pain.

Joint tenderness was assessed as present or absent. The mobility of the joint was graded on the basis of ordinal scale: 0 = no movement joint ankylosed, 1 = extremely hypomobile, 2 = slightly hypomobile, 3 = normal, 4 = slightly hypermobile, 5 = extremely hypermobile, and 6 = unstable.

Lastly, time needed for the patient to be symptom free on each visit was reported.

Evaluation of safety was depending on the occurrence of any adverse event and was graded based on the severity, onset, and the course of adverse effects.

The global assessment of efficacy of treatment was conducted by the physicians and patients at the end of the study based on the scale: 1 = very good improvement, 2 = good improvement, 3 = moderate improvement, and 4 = negligible improvement, and tolerability was assessed depending on the scale: 1 = excellent, 2 = good, 3 = fair, and 4 = poor.

Statistics
The data were pooled, and the results were analyzed using parametric and nonparametric tests. All the tests were two-tailed, and \( P < 0.05 \) was considered statistically significant.

RESULTS

Demographic profile
A total of 442 cases were evaluated in the study. The overall demographic profile of the patients is presented in Table 1. The physical examination parameters such as temperature, pulse rate, and respiratory rate were within the normal limits at the baseline, as shown in Table 2.

Effect on pain intensity
The mean visual analog score was 6.5 at the first visit (baseline). After the treatment at the end of 1 week (second visit), the mean visual analog score was 3.77. At the end of the study, i.e., after 2 weeks, the mean visual analog score further reduced to 0.67. After 1 and 2 weeks, there was a significant fall in the pain score of 42% and 90%, respectively, from the baseline, \( P < 0.05 \) [Figure 1].

Change in percentage of joint tenderness
Tenderness was present in 399 patients at the first visit, i.e., before the treatment, which significantly reduced to 255 (63.90%) and 40 (10.02%) patients after the 1st and 2nd weeks of the treatment, respectively [Figure 2].

Effect on joint mobility
The mean joint mobility score was 1.06 at the first visit (baseline). After the treatment at the end of 1 week, the mean joint mobility score was increased to 1.97. At the end of 2 weeks (third visit), the mean joint mobility score was 2.78. There is a significant increase in the mean joint mobility score from 1.06 to 2.78 (\( P < 0.05 \)) at the end of the treatment [Figure 3].

Time needed by the patient to be symptom free
Of the 442 patients in this study, 24 patients (5.42%) became symptom free at the end of the 1st week (second visit) and 418 patients (94.57%) at the end of the treatment [Figure 4].

Global assessment of the efficacy of treatment
As per the physicians’ evaluation, 66.29% of the cases showed very good efficacy, 28.51% showed good efficacy, and 4.98%

| Table 1: Demographic data |
|---------------------------|
| **Parameters** | **Numbers** |
| Number of cases | 442 |
| Age (years) | Mean±SD 37.84±9.28 |
| Range | 18-55 |
| Weight (kg) | Mean±SD 65.76±8.989 |
| Range | 38-86 |
| Sex (%) | Male 275 (62.22) Female 167 (37.78) |

| SD: Standard deviation |

| Table 2: Profile of physical examination |
|------------------------------------------|
| **Physical examination** | **Mean±SD (n = 442)** |
| Temperature (°F) | 98.30±0.55 |
| Pulse rate (/min) | 77.55±5.06 |
| Respiratory rate (/min) | 17.73±2.83 |

SD: Standard deviation
and 0.22% satisfactory and unsatisfactory, respectively, after the treatment [Figure 5a]. According to the patients’ evaluation, 57.47% of the patients had very good effect of treatment, 36.20% had good improvement, 6.11% had satisfactory, and 0.22% had unsatisfactory effect after the treatment [Figure 5b].

**Global assessment of the tolerability of treatment**

As per the physicians’ evaluation, 80.54% of the cases had excellent tolerability and 19.46% cases had good tolerability [Figure 6a]. According to the patients’ evaluation, 79.19% had excellent tolerability and 20.81% had good tolerability [Figure 6b].

**Safety assessment**

In the present study, 13.34% of the total cases had adverse events [Table 3]. Of these, the most common adverse events were gastrointestinal side effects and nausea followed by giddiness, heartburn, headache, dizziness, diarrhea, and fever. The intensity of events was mild in most of the cases, which resolved without withdrawal of the drug. No serious adverse events were observed during the study period, and not a single patient had withdrawn or discontinued the treatment due to adverse events.

**DISCUSSION**

Modified release aceclofenac formulation in comparison with conventional tablets has demonstrated comparable efficacy with lesser side effects in patients suffering from knee osteoarthritis. The requirement of concomitant medications such as ranitidine and acetaminophen was also less in the patients who received modified release aceclofenac as compared to conventional aceclofenac tablets. The report concluded that the modified release form of aceclofenac was found to be effective and safe while offering the practical advantage of single-dose administration with fewer side effects. Another study evaluating the controlled release formulation and immediate release formulation of aceclofenac demonstrated equal efficacy and safety in both the study groups.[21] Modified release formulations could be

| Table 3: Profile of adverse events |
|----------------------------------|
| **Adverse events** | **Percentage of patients** |
| Gastro intestinal side effects | 8.82 |
| Nausea | 1.58 |
| Giddiness | 0.90 |
| Heartburn | 0.67 |
| Headache | 0.45 |
| Dizziness | 0.45 |
| Diarrhea | 0.22 |
| Fever | 0.22 |
| **Total** | 13.34 |

![Figure 3: Effect on the joint mobility score](image1)

![Figure 4: Time needed by the patients to be symptom free](image2)

![Figure 5: Overall global assessment of efficacy by physicians (a) and patients (b)](image3)
a potential option for elevating the patient compliance with no compromise on efficacy and safety.

Our results indicate that the combination of thiocolchicoside and aceclofenac in sustained-release form is effective in the management of pain due to inflammation and muscle spasm. The combination is safe as the result reveals that only a few patients had adverse events, and the intensity of events was mild in most of the cases, which resolved during the treatment. The most common adverse events were gastrointestinal side effects and nausea followed by dizziness, headache, dizziness, diarrhea, and fever. The tolerability of the treatment was observed to be good to excellent as per the physicians and patients assessment, respectively. Hence, this combination is safe and is well tolerated for the treatment of patients with acute inflammatory conditions associated with spasm.

Various clinical trials have demonstrated better efficacy of combination therapy in comparison with the single agent in musculoskeletal inflammatory conditions associated with pain. The pain score reduction is more pronounced with the combination of thiocolchicoside and aceclofenac as compared to aceclofenac alone. This combination is useful in the treatment of low back pain in clinical practice.[23] Thiocolchicoside and aceclofenac combination has been reported to be well tolerated in patients with severe back pain without any side effect of sedation or seizures.[21] Thiocolchicoside and aceclofenac combination is preferred in patients with low back pain associated with muscle spasm. This combination showed better clinical improvement and had better safety profile than a combination of aceclofenac, chlorzoxazone, and paracetamol.[12] Thus, several findings are in line with the current study demonstrating significant pain reduction associated with inflammation and muscle spasm.

This study also demonstrated the efficacy of the combination in improving the joint tenderness. The joint stiffness is one of the major factors linked with inflammation, muscle spasm, and pain. Significant normalization of joint motility is evident in the current study after the administration of the fixed-dose combination of thiocolchicoside and aceclofenac in sustained-release form. Nearly all the patients were free from symptoms at the end of the treatment regimen. The combination was well tolerated with no major adverse effects experienced by the patients.

**CONCLUSIONS**

The postmarketing surveillance confirms the use of fixed-dose combination of thiocolchicoside and aceclofenac in sustained-release form, as the potential therapy for the treatment of patients suffering with acute musculoskeletal inflammatory conditions associated with pain. The efficacy is very good in most of the patients, and the therapy is found to be tolerable with no serious safety concerns.

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**Conflicts of interest**

There are no conflicts of interest.

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