Section: Miscellaneous

Original Research Article

EFFICACY AND SAFETY OF A FIXED-DOSE COMBINATION OF CHLORZOXAZONE, DICLOFENAC POTASSIUM, AND PARACETAMOL COMPARED WITH DICLOFENAC POTASSIUM AND PARACETAMOL IN ACUTE MUSCULOSKELETAL SPASM: A MULTICENTER RANDOMIZED PHASE IV STUDY

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ABSTRACT

Background: Acute musculoskeletal spasm is a common clinical condition associated with pain, stiffness, and functional impairment, significantly affecting quality of life and daily activities. Conventional treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol may not adequately address the underlying muscle spasm conditions, highlighting the need for multimodal therapeutic approaches. The objective is to evaluate the efficacy and safety of a fixed-dose combination of chlorzoxazone, diclofenac potassium, and paracetamol compared with diclofenac potassium and paracetamol in patients with acute musculoskeletal spasm.

Materials and Methods: This Phase IV, prospective, randomized, open label, multicentric comparative study enrolled 200 patients across five centres. Patients were randomized (1:1) to receive either chlorzoxazone 500 mg + diclofenac potassium 50 mg + paracetamol 325 mg or diclofenac potassium 50 mg + paracetamol 325 mg, administered orally twice daily for 5 days. Primary efficacy endpoints included changes in pain intensity at rest and during passive movement using the Numeric Rating Scale (NRS), muscle spasm score, and global assessments by patients and physicians. Safety was evaluated through monitoring of adverse events.

Results: Of the 200 patients enrolled, 196 completed the study. By Day 5, significantly more patients in the FDC group achieved complete pain relief at rest (62.89% vs. 25.25%) and during movement (52.58% vs. 15.15%) compared to the comparator group ($p < 0.001$). Complete resolution of muscle spasm was higher in the FDC group (74.23% vs. 38.38%; $p < 0.001$). Global assessments favored the FDC ($p < 0.01$). Adverse events were low and comparable, with no serious events.

Conclusion: The chlorzoxazone-based FDC demonstrated superior efficacy with comparable safety, providing an effective option for acute musculoskeletal spasm.

Keywords: Acute musculoskeletal spasm; Chlorzoxazone; Diclofenac potassium; Paracetamol; Randomized clinical trial; Muscle relaxants.

INTRODUCTION

Acute musculoskeletal spasm is a common clinical condition encountered in routine medical practice, characterized by involuntary muscle contraction, pain, stiffness, and functional limitation. It is frequently associated with conditions such as low back pain, cervical strain, and soft tissue injuries, and contributes significantly to reduced quality of life and work productivity. Epidemiological data suggest that musculoskeletal disorders are among the leading causes of disability worldwide, with acute painful spasms representing a substantial proportion of outpatient visits in both primary care and orthopaedic settings.[1]

The management of acute musculoskeletal spasm primarily focuses on alleviating pain, reducing muscle stiffness, and restoring functional mobility. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are commonly used as first-line therapies due to their well-established analgesic and anti-inflammatory properties. However, these agents may not adequately address the underlying muscle spasm component, which plays a critical role in pain perpetuation and functional impairment. Consequently, monotherapy with analgesics often results in suboptimal clinical outcomes, necessitating the use of adjunctive therapies.[2]

Skeletal muscle relaxants, such as chlorzoxazone, act centrally to reduce muscle hyperactivity and have been shown to provide additional symptomatic relief when combined with analgesics. The pharmacological rationale for combining a muscle relaxant with an NSAID and paracetamol lies in their complementary mechanisms of action. While diclofenac exerts its effect through inhibition of cyclooxygenase enzymes and reduction of inflammatory mediators, paracetamol provides central analgesia, and chlorzoxazone reduces muscle spasm through central nervous system modulation. This multimodal approach is hypothesized to result in enhanced pain relief and faster functional recovery compared to analgesic therapy alone.[3]

Despite the widespread clinical use of such fixed-dose combinations (FDCs), there remains a relative paucity of robust post-marketing, real-world evidence evaluating their comparative efficacy and safety. Most existing studies are limited by small sample sizes, heterogeneous patient populations, or lack of direct comparison with standard analgesic regimens. Given the increasing emphasis on evidence-based prescribing and rational pharmacotherapy, there is a need for well-designed Phase IV clinical studies to validate the clinical benefits of these combinations in routine practice settings.[4]

In this context, the present study was conducted to evaluate the efficacy and safety of a fixed-dose combination of chlorzoxazone, diclofenac potassium, and paracetamol compared with diclofenac potassium and paracetamol in patients with acute musculoskeletal spasm. The primary objective was to assess improvement in pain intensity and muscle spasm, while the secondary objective was to evaluate the safety and tolerability profile of the Study group combination in a multicentric, randomized clinical setting.[5]

MATERIALS AND METHODS

Study Design and Setting: This was a Phase IV, prospective, randomized, open-label, multicentre, comparative clinical study conducted to evaluate the efficacy and safety of a fixed-dose combination of chlorzoxazone, diclofenac potassium, and paracetamol in patients with acute musculoskeletal spasm. The study was carried out across five tertiary care centres in India, ensuring representation of diverse patient populations and routine clinical practice settings. Each participant completed a 5-day study period, followed by a safety assessment during the follow-up.[6]

Ethical Considerations: The study was conducted accordance with IEC Approved Protocol, relevant SOPs, Drugs and Cosmetics Act 1940, New Drugs and Clinical Trials Rules, 2019 [Gazette Notification G.S.R.227 (E), Dated 19.03.2019], Ethical guidelines for biomedical research on human patients, Indian Council of Medical Research (2017), ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2) Guideline for Good Clinical Practice (2016), Good Clinical Laboratory practices (GCLP), Declaration of Helsinki (Brazil, October 2013) and other applicable Regulatory Requirements. The study protocol and amendments to the protocol, patient information sheet, consent form and other study specific documents were submitted to the IEC, registered with CDSCO. This study was initiated after the protocol was reviewed and approved by the concerned IEC. The current trial was registered on Clinical Trials Registry-India (CTRI), before enrolment of the first patient in the study (CTRI Registration No. CTRI/2023/08/056872).[7]

Study Population

Inclusion Criteria

Patients were included if they matched the following criteria:

- Male or female patients aged 18 to 65 years
- Clinical diagnosis of acute musculoskeletal spasm
- Presence of muscle pain with a Numeric Rating Scale (NRS) score ≥4 at rest
- Muscle spasm score indicating clinically significant spasm
- Ability and desire to give written informed permission and follow research procedures

Exclusion Criteria

Patients were excluded if they had:

- History of hypersensitivity to any of the study drugs.
- Severe cardiac, hepatic, gastrointestinal, or pulmonary disorders

- Requirement of parenteral therapy, surgery, or hospitalization for spasm management
- Use of analgesic or anti-inflammatory medications within 48 hours prior to enrolment
- Participation in another clinical trial within the previous 90 days
- Pregnant or lactating women, or any condition deemed unsuitable by the investigator

These criteria ensured the inclusion of a homogeneous population suitable for assessing therapy efficacy and safety.[8]

Randomization and Treatment Allocation

Eligible patients were randomized in a 1:1 ratio to either the experimental or comparator goods. Randomization was performed using an electronic data gathering equipment that generated unique allocation codes to ensure equitable assignment. Because the interventions involved marketed commodities, the trial employed an open-label design with no blinding.[9]

Interventions

Patients in the Study group received a fixed-dose combination of chlorzoxazone 500 mg, diclofenac potassium 50 mg, and paracetamol 325 mg, while patients in the comparator group received diclofenac potassium 50 mg and paracetamol 325 mg. All medications were administered orally, twice daily, for a duration of 5 days. A minimum of 8 hours was allowed between dosages. Patients were instructed to adhere strictly to the prescribed dosing schedule, and compliance was monitored through patient diaries and drug accountability records.

Outcome Measures

Efficacy Endpoints

The primary efficacy endpoints included:

- Change in muscle pain intensity at rest, assessed using the Numeric Rating Scale (NRS)
- Change in pain intensity during the Numeric Rating Scale (NRS; 0–10, where 0 = no pain and 10 = worst imaginable pain)
- Improved muscular spasm score based on clinical examination
- A comprehensive evaluation of therapy response by physicians and patients.

Assessments were performed at baseline (Day 1), Day 3, and Day 5 to track treatment response over time.[10]

Safety Endpoints

Safety was evaluated through monitoring of treatment-emergent adverse events (TEAEs), clinical laboratory parameters, and vital signs. Laboratory investigations included haematological and biochemical parameters such as complete blood count, liver function tests, renal function tests, and bilirubin levels. Adverse events were recorded during the trial and categorized based on severity and relevance to the study drug.[7]

Statistical Analysis: The sample size was designed to ensure adequate power to detect clinically significant differences between treatment groups. Continuous variables were summarized using mean, standard deviation, and median values, and categorical variables were represented using frequencies and percentages.

Comparative studies between treatment groups were conducted using appropriate statistical procedures, such as the Cochran-Mantel-Haenszel test for ordinal outcomes and chi-square testing for categorical data. Paired t-tests were used to examine changes within the groups over time.

A p-value of <0.05 indicated statistical significance. The per-protocol population was analysed for efficacy, while the intention-to-treat group was analysed for safety. To ensure that the data were accurate and reliable, statistical analyses were performed using established statistical software.[10]

RESULTS

Patient Disposition: A total of 200 patients were enrolled and randomized equally into the Study group and comparator groups (n = 100 each). Of these, 196 patients completed the study as per protocol, with 97 patients in the Study group and 99 patients in the comparator group. Four patients were lost in follow-up (three in the Study group and one in the comparator group). All randomized patients were included in the safety analysis (intention-to-treat population), while efficacy analyses were performed on the per-protocol population. The details of patient disposition are summarized in [Table 1].

Table 1: Patient Disposition

Parameter	Study group (n=100)	Comparator group (n=100)	Total (n=200)
Enrolled	100	100	200
Completed	97 (97%)	99 (99%)	196 (98%)
Discontinued	3 (3%)	1 (1%)	4 (2%)
Lost to follow-up	3 (3%)	1 (1%)	4 (2%)

Baseline Demographic and Clinical Characteristics: Baseline demographic and clinical characteristics were comparable between the two treatment groups. The mean age of patients in the Study group was 35.63 ± 11.13 years, while in the comparator group it was 34.35 ± 10.27 years. The gender distribution was similar, with 61% males and 39% females in the Study group and 59% males and 41% females in the comparator group. Body mass index (BMI), height, and weight were also comparable across both groups, indicating homogeneity of the study population at baseline. The baseline characteristics of the study population are presented in [Table 2].

Table 2: Baseline Characteristics

Parameter	Study group	Comparator group
Age (years, mean ± SD)	35.63 ± 11.13	34.35 ± 10.27
Male (%)	61%	59%
Female (%)	39%	41%
BMI (kg/m²)	24.35 ± 4.26	24.74 ± 3.54
Weight (kg)	63.99 ± 14.23	65.68 ± 10.35
Height (cm)	161.70 ± 9.32	162.99 ± 9.09

Pain Intensity Outcomes

Pain at Rest (NRS): At baseline, the majority of patients in both groups reported moderate to severe pain. By Day 5, a significantly greater proportion of patients in the Study group reported no pain compared with the comparator group (62.89% vs. 25.25%). Additionally, only 1.03% of patients in the Study group reported moderate pain at Day 5, compared with 8.08% in the comparator group. The difference between groups was statistically significant ($p < 0.001$), indicating superior pain relief with the Study group treatment. The Study group combination chlorzoxazone + diclofenac potassium + paracetamol demonstrated superior pain relief compared to diclofenac + paracetamol alone in acute musculoskeletal spasm. A higher proportion of patients achieved complete pain relief by Day 5, indicating faster and more complete pain relief at rest and during movement. These findings indicate statistically significant improvement ($p < 0.001$) and demonstrate faster and more effective analgesia both at rest and during functional activity. The distribution of pain intensity at rest is presented in [Table 3], and the comparative pattern between treatment groups is illustrated in [Figure 1].

Table 3: Pain at Rest (Day 5)

Category	Study group (%)	Comparator group (%)
No pain	62.89	25.25
Mild pain	36.08	66.67
Moderate pain	1.03	8.08
Severe pain	0	0

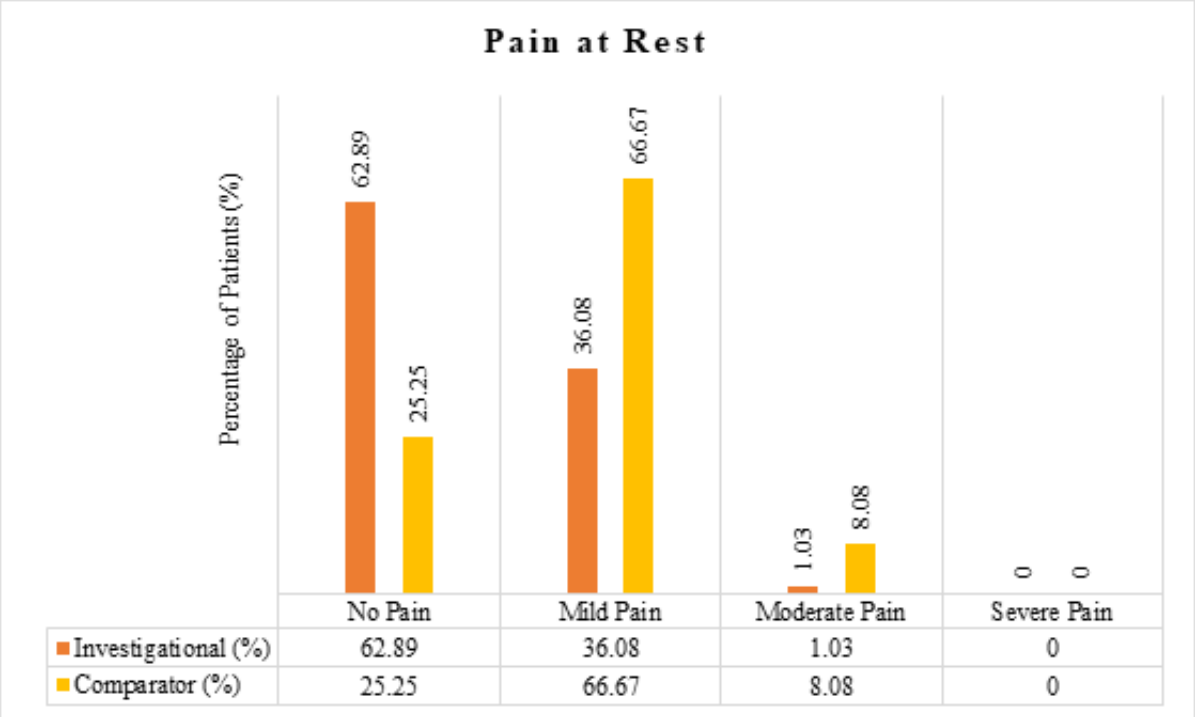

Figure 1: Pain at Rest (Day 5)

Pain During Passive Movement (NRS): Similar trends were observed for pain during passive movement. At Day 5, 52.58% of patients in the Study group reported no pain compared with 15.15% in the comparator group. Moderate pain was reported by only 4.12% of patients in the Study group, whereas 17.17% of patients in the comparator group continued to experience moderate pain. These differences were statistically significant ($p < 0.001$), demonstrating greater improvement in functional pain outcomes with the Study group combination. The Study group treatment supports improved

functional recovery in acute musculoskeletal conditions. The lower proportion of patients with residual moderate pain reflects improved mobility and functional outcomes, which are clinically more meaningful than pain at rest alone. The distribution of pain during passive movement is presented in [Table 4], and the between-group comparison is illustrated in [Figure 2].

Table 4. Pain During Passive Movement (Day 5)

Category	Study group (%)	Comparator group (%)
No pain	52.58	15.15
Mild pain	43.3	67.68
Moderate pain	4.12	17.17
Severe pain	0	0

Muscle Spasm Assessment

At baseline, most patients in both groups exhibited moderate to severe muscle spasm. By Day 5, a marked reduction in muscle spasm severity was observed in both groups; however, the improvement was significantly greater in the Study group. A total of 74.23% of patients in the Study group reported complete resolution of muscle spasm compared with 38.38% in the comparator group. No patients in the Study group had moderate or severe spasm at Day 5, whereas 14.14% of patients in the comparator group continued to exhibit moderate spasm. The difference between groups was statistically significant ($p < 0.001$). The Study group combination was clinically superior in relieving muscle spasm, demonstrating a higher rate of complete resolution and no moderate or severe spasm at Day 5, indicating direct action on the underlying spasm rather than pain masking. The distribution of muscle spasm severity is summarized in [Table 5], and the reduction pattern across categories is illustrated in [Figure 3].

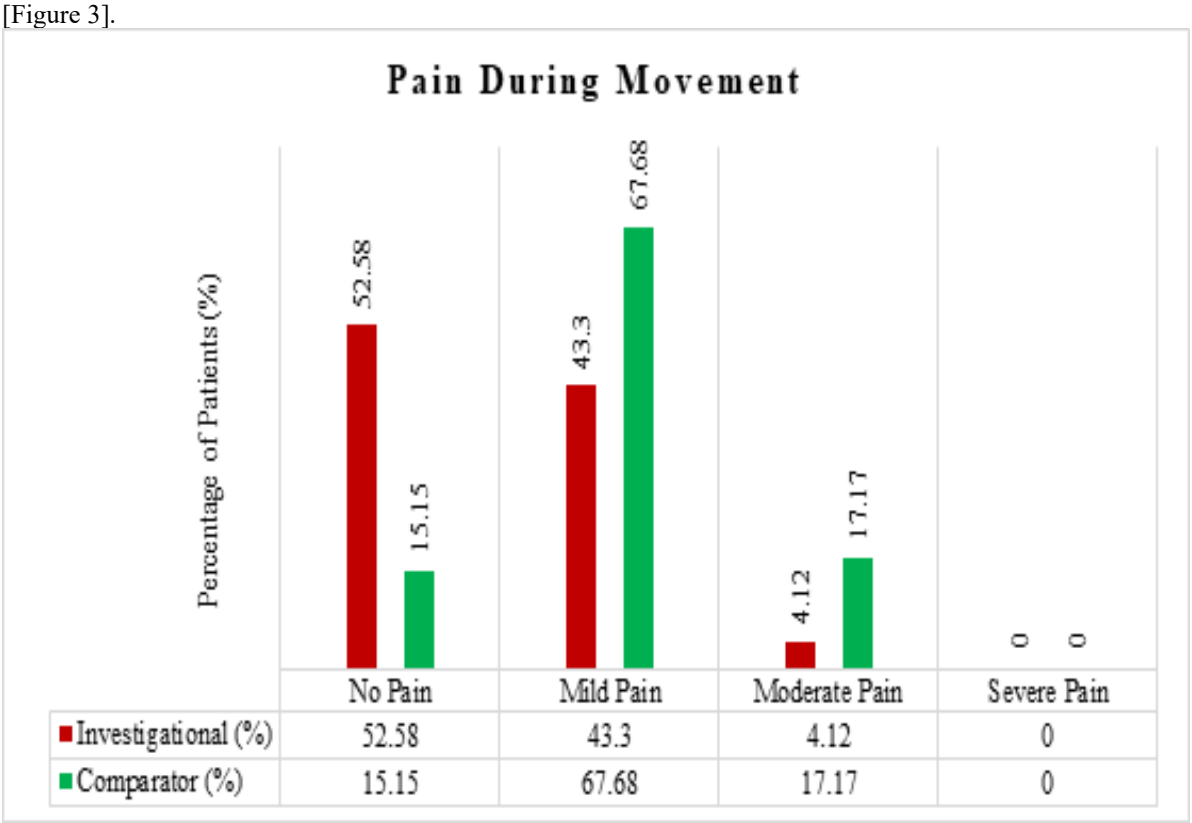

Figure 2: Pain During Passive Movement (Day 5)

Table 5: Muscle Spasm Score (Day 5)

Category	Study group (%)	Comparator group (%)
No spasm	74.23	38.38
Mild spasm	25.77	47.47
Moderate spasm	0	14.14
Severe spasm	0	0

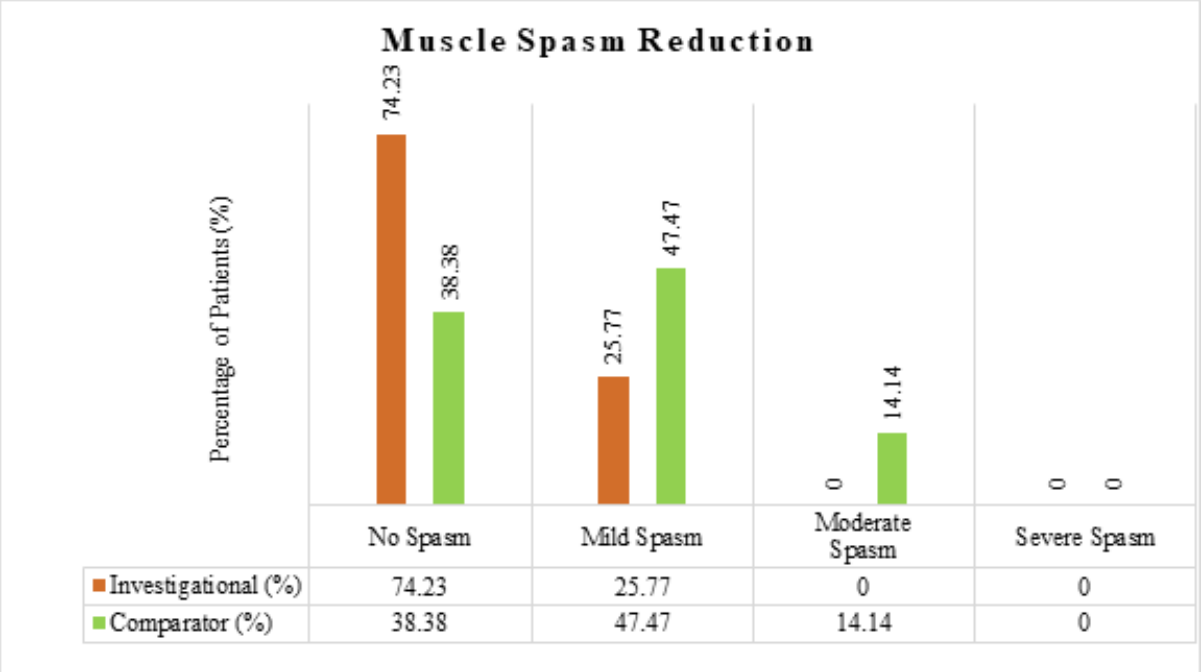

Figure 3: Muscle Spasm Reduction (Day 5)

Patient Global Assessment

Patient-reported outcomes demonstrated substantial improvement in both groups, with significantly greater improvement observed in the Study group. By Day 5, 68.04% of patients in the Study group were categorized as "very much improved" compared with 38.38% in the comparator group. Conversely, a higher proportion of patients in the comparator group remained in the "minimally improved" category (18.18% vs. 4.12%). These differences were statistically significant, indicating superior patient-perceived outcomes with the Study group treatment ($p < 0.01$). A higher proportion of patients reported 'very much improved' outcomes, indicating enhanced overall patient-perceived recovery and satisfaction. The patient global assessment outcomes are presented in [Table 6], and the comparative distribution is illustrated in [Figure 4].

Table 6. Patient Global Assessment (Day 5)

Outcome	Study group (%)	Comparator group (%)
Very much improved	68.04	38.38
Much improved	26.8	39.39
Minimally improved	4.12	18.18
No change	1.03	4.04

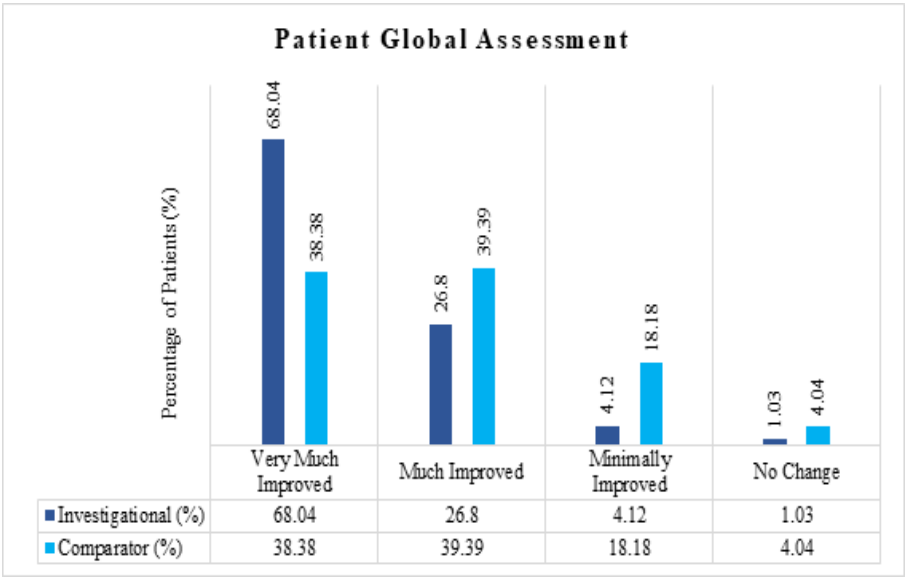

Figure 4: Patient Global Assessment (Day 5)

Physician Global Assessment: Physician assessments were consistent with patient-reported outcomes. At Day 5, 73.20% of patients in the Study group were rated as "very much improved" compared with 41.41% in the comparator group. Additionally, fewer patients in the Study group were categorized as "minimally improved" (3.09%) compared with the comparator group (15.15%). These findings were statistically significant ($p < 0.01$), confirming the enhanced clinical effectiveness of the Study group combination. The Study group treatment was rated as highly effective by physicians in a significantly greater proportion of patients, confirming clinical superiority from the physician perspective and demonstrating clinically meaningful benefits in real-world practice settings. The physician global assessment results are summarized in [Table 7], and the corresponding comparison is illustrated in [Figure 5].

Table 7: Physician Global Assessment (Day 5)

Outcome	Study group (%)	Comparator group (%)
Very much improved	73.2	41.41
Much improved	22.68	40.4
Minimally improved	3.09	15.15
No change	1.03	3.03

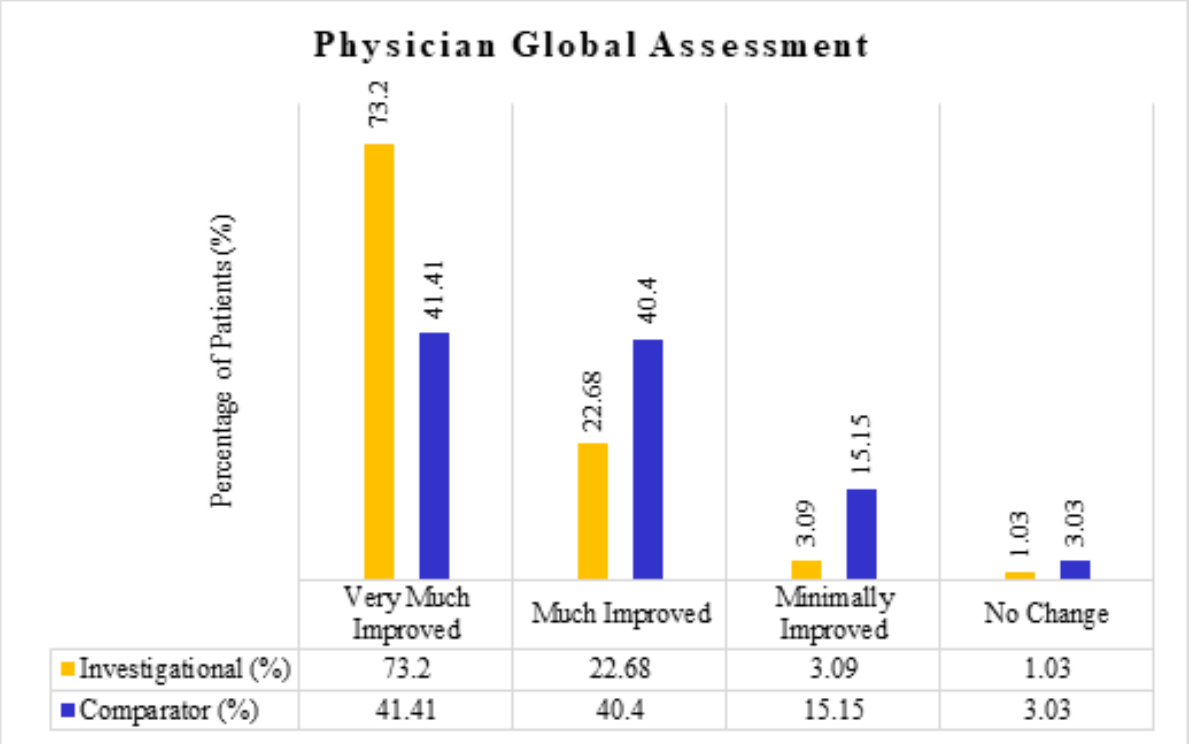

Figure 5: Physician Global Assessment (Day 5)

Safety Outcomes: Safety analysis included all 200 randomized patients. The overall incidence of treatment-emergent adverse events (TEAEs) was comparable between groups, occurring in 7% of patients in the Study group and 8% in the comparator group. No serious adverse events or deaths were reported during the study. The overall safety outcomes are summarized in Table 8, while the distribution of commonly reported adverse events is presented in [Table 9].

The most reported adverse events included nausea, dyspepsia, dizziness, asthenia, and vomiting. All adverse events were mild in severity and resolved with standard care. The incidence and nature of adverse events were similar between the two treatment groups, indicating a comparable safety profile. The Study group combination was well tolerated with a safety profile comparable to standard therapy. There was no increase in adverse events despite enhanced efficacy, and no additional safety burden was observed, with all adverse events being mild and self-limiting.

Table 8: Adverse Events Summary (Day 5)

Parameter	Study group (%)	Comparator group (%)
Any AE	7	8
Serious AE	0	0

Table 9: Common Adverse Events (Day 5)

Event	Study group (%)	Comparator group (%)
Nausea	3	1
Dyspepsia	1	4
Dizziness	1	1
Asthenia	1	1
Vomiting	1	0

The Study group combination demonstrated rapid and consistent response across multiple endpoints, including pain (at rest and during movement), muscle spasm, and global assessments by both patients and physicians. These findings indicate robust, multidimensional and consistent efficacy across multiple clinical endpoints.

DISCUSSION

The present multicentric, randomized Phase IV study demonstrated that the fixed-dose combination of chlorzoxazone, diclofenac potassium, and paracetamol provides superior efficacy in reducing pain intensity and muscle spasm compared with diclofenac potassium and paracetamol alone in patients with acute musculoskeletal spasm. These improvements were consistently observed across multiple endpoints, including pain at rest, pain during passive movement, muscle spasm scores, and both patients and physician reported global assessments, while maintaining a comparable safety profile.

The enhanced analgesic efficacy observed in the Study group can be attributed to the complementary pharmacological mechanisms of the three agents. Diclofenac exerts anti-inflammatory effects through inhibition of cyclooxygenase-mediated prostaglandin synthesis, thereby reducing peripheral inflammation. Paracetamol acts centrally to modulate pain perception, while chlorzoxazone, a centrally acting skeletal muscle relaxant, reduces muscle hyperactivity by acting at the level of the spinal cord and brain. This multimodal mechanism enables simultaneous targeting of inflammation, central pain pathways, and muscle spasm, resulting in more comprehensive symptom relief compared with diclofenac and paracetamol therapy alone.[11] The Study group combination represents a rational multimodal combination targeting pain, inflammation, and muscle spasm. By combining central muscle relaxation with potent analgesic and anti-inflammatory action, it effectively breaks the pain–spasm cycle, leading to comprehensive symptom control.

A key finding of the present study was the significant improvement in pain during passive movement, which reflects functional recovery rather than symptomatic relief alone. This observation highlights the importance of addressing muscle spasm as a core pathophysiological component in acute musculoskeletal conditions. Persistent muscle spasm can perpetuate a pain–spasm cycle, leading to restricted mobility and delayed recovery. The addition of chlorzoxazone likely interrupts this cycle, contributing to the greater functional improvement observed in the Study group.[12]

The findings of this study are consistent with previously published evidence supporting the use of combination therapy in musculoskeletal disorders. Clinical studies evaluating muscle relaxant combinations have reported faster onset of pain relief and greater reduction in muscle stiffness compared with NSAID monotherapy. Chlorzoxazone-based combinations have demonstrated improved patient-reported outcomes and enhanced functional recovery in conditions such as acute low back pain and cervical spasm, reinforcing the clinical relevance of the present findings.[13]

The superiority of the Study group combination was further supported by global assessment outcomes. A substantially higher proportion of patients in the Study group were categorized as “very much improved” by both patients and physicians. These outcomes are clinically meaningful, as global assessments reflect overall patient well-being, functional improvement, and satisfaction with treatment. The concordance between patient-reported and physician-evaluated outcomes strengthens the reliability of the observed treatment effect.[14]

Importantly, the improved efficacy did not result in an increased incidence of adverse events. The overall frequency of treatment-emergent adverse events was low and comparable between the two groups, and no serious adverse events were reported. All adverse events were mild in nature and resolved with standard care. These findings are consistent with the established safety profiles of the individual components and suggest that the addition of chlorzoxazone does not compromise tolerability when used in combination therapy.[15]

The present study has several strengths that enhance the validity and generalizability of its findings. The randomized, multicentric design reduces selection bias and increases external validity. The inclusion of both patient-reported and physician-assessed outcomes provides a comprehensive evaluation of treatment effectiveness. Additionally, the study reflects real-world clinical practice, as it was

conducted in routine care settings with commonly used therapeutic regimens.

However, certain limitations should be acknowledged. The open-label design may introduce potential bias in subjective outcome assessment, although the consistency between objective and subjective endpoints mitigates this concern to some extent. The relatively short duration of treatment (5 days) limits the assessment of long-term efficacy and safety.

Overall, the findings of this study support the use of a multimodal therapeutic approach targeting both pain and muscle spasm in the management of acute musculoskeletal conditions. The addition of a centrally acting muscle relaxant to standard analgesic therapy appears to provide clinically meaningful benefits without compromising safety.

CONCLUSION

In conclusion, the fixed-dose combination of chlorzoxazone, diclofenac potassium, and paracetamol demonstrated statistically significant and clinically meaningful superiority compared with diclofenac potassium and paracetamol alone in the management of acute musculoskeletal spasm. The Study group combination provided greater reductions in pain intensity at rest and during movement, along with more rapid and complete resolution of muscle spasm.

These improvements translated into better functional recovery, as evidenced by significant improvement in movement-related pain outcomes and enhanced both patient-reported and physician-assessed global outcomes, indicating meaningful clinical benefit.

Importantly, the enhanced efficacy was achieved without an increase in adverse events, with both treatment groups exhibiting comparable safety profiles and only mild, self-limiting adverse effects. This demonstrates a favorable benefit–risk profile and indicates no additional safety burden despite higher efficacy.

Overall, the Study group combination provides faster and more complete pain relief, supports improved functional recovery, and delivers consistent efficacy across multiple clinical endpoints. These findings support the clinical advantage of a multimodal therapeutic approach that effectively breaks the pain–spasm cycle and establishes this combination as an effective and well-tolerated option for the management of acute musculoskeletal spasm.

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