

# Effect of Tolperisone a Muscle Relaxant in the Management of Musculoskeletal Disorders in the Population of Central India

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## ABSTRACT

**Background:** Drugs like skeletal muscle relaxants produce reversible skeletal muscle relaxation. Skeletal muscle function and muscle tone are affected by muscle relaxants. Tolperisone a piperidine derivative is a centrally-acting skeletal muscle relaxant with membrane-stabilizing properties and under clinical use for decades. It provides more than 75% improvement in spastic disorders. This study aims to be carried out to observe the effect of Tolperisone as a muscle relaxant in various musculoskeletal disorders and to find out any adverse effects it produces.

**Methods:** In the present clinical study, 299 patients, aged between 21 and 65 years with various kinds of musculoskeletal disorders participated. Before enrollment of the cases, musculoskeletal disorders were diagnosed by clinical examinations and various investigations such as X-Ray, MRI, RA factor, Uric acid, anti-CCP, CRP, ESR, etc. depending upon the history and clinical examinations. Confirmed cases of musculoskeletal disorders were treated by giving Tolperisone 150 mg thrice daily for 5 to 10 days. After 5-10 days, a clinical examination was done and a self-administered questionnaire was given for subjective responses.

**Results:** Based on clinical examinations and subjective response, all 299 cases got symptomatic relief from the signs and symptoms. The range of relief was between 80-100%. No adverse effect was reported except in one case where metallic taste was reported.

**Conclusion:** It can be concluded that Tolperisone at the dose of 150 mg is a good and safe muscle relaxant for various musculoskeletal disorders.

**Key-words:** Tolperisone, Muscle relaxant, Muscle spasm, Musculoskeletal Disorders, Non-steroidal inflammatory drugs.

## INTRODUCTION

Skeletal muscle relaxants are used to produce reversible skeletal muscle relaxation. Skeletal muscle function and muscle tone are affected by muscle relaxants. Various musculoskeletal disorders and a variety of

spastic disorders are treated by using these drugs. These drugs are also used to treat muscle spasms, pain and hyperreflexia. Non-steroidal inflammatory drugs (NSAIDs) or centrally acting skeletal muscle relaxants were used to manage the symptoms of musculoskeletal disorders (locomotor). Unfortunately, acting drugs produce sedation or depression, whereas NSAIDs have adverse gastric tolerability <sup>[1-3]</sup> In the category of centrally acting drugs, many drugs are available as centrally acting muscle relaxants but they have many disadvantages including sedation and central nervous system depression etc. <sup>[2]</sup> Baclofen a centrally acting muscle relaxant produces adverse drug reactions like ataxia,

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weakness, mental confusion and drowsiness. It increases the serum transaminase level. chronic use of baclofen causes sudden withdrawal symptoms like seizures, tachycardia and hallucinations.<sup>[2]</sup>

Tolperisone a piperidine derivative is a centrally-acting skeletal muscle relaxant with membrane-stabilizing properties and under clinical use for decades. It is a good muscle relaxant.<sup>[4]</sup> The advantage of the use of Tolperisone is; it provides more than 75% improvement in spastic disorders while having limited side effects. Some of the adverse effects recorded are muscle pain, generalized body weakness, and dizziness which are self-limiting and do not require discontinuation of the treatment.<sup>[3,5]</sup>

Individual studies regarding the use of Tolperisone in multiple musculoskeletal disorders are very few as per our best knowledge and extensive search although individual studies on individual disorders are available like the use of Tolperisone in spasticity by various authors in various other countries on different populations.<sup>[6]</sup> Lindsay *et al.*<sup>[7]</sup> in their systemic review regarding Pharmacological interventions for drugs other than botulinum toxin used for spasticity after stroke. Drugs other than botulinum had lack of high-quality randomized clinical trials for their review. Systemic antispasmodics are not so effective in improving spasticity related to stroke.

Agarwal *et al.*<sup>[6]</sup> observed that the overall efficacy of Tolperisone was greater than Baclofen in patients with spasticity disorder due to upper motor neuron syndrome. Moreover, they also observed that Baclofen has more side effects in comparison to Tolperisone. Stamenova *et al.*<sup>[8]</sup> studied the efficacy and safety of the Tolperisone drug. They found that Tolperisone had high efficacy and excellent tolerance in the treatment of spastic hypertonia following cerebral stroke. However, as per their opinion, the individual dose titration may exceed the recommended maximum dose of 450 mg daily to get optimized therapeutic benefit. Kaplunov *et al.*<sup>[9]</sup> compared the efficacy of the standard treatment protocol in osteoarthritis with the modified protocol with the addition of Tolperisone and observed the superiority and best results of the addition of Tolperisone in the management of osteoarthritis.

The present study was conducted to assess the effect of Tolperisone as a muscle relaxant in various musculoskeletal disorders and to discover any adverse

effects it produces. It is a clinical and questionnaire-based study in which the outcome was assessed based on clinical evaluation. A self-administered questionnaire was given to the patients to record subjective responses.

## MATERIALS AND METHODS

In the present clinical study, 299 patients, aged between 21-65 years with various kinds of musculoskeletal disorders participated after giving written informed consent. Participants were from Nagpur city which is a central Indian city and hub of medical facilities and surrounding areas including various parts of other central Indian regions. Among the participants, 194 (65%) were male while 105 (35%) patients were female. The study period was from September 2021 to December 2022.

**Methodology-** Before enrollment of the cases, musculoskeletal disorders were diagnosed by clinical evaluation such as straight leg raising test in case of disc prolapse, etc., and by various investigations such as X-ray, MRI, RA factor, Uric acid, Anti-CCP, CRP, ESR, etc. depending upon the history and clinical examinations of individual cases.

Confirmed cases of musculoskeletal disorders were treated by giving Tolperisone 150 mg three times a day for 5-10 days. Tolperisone provides relief from the muscle spasm, muscle stiffness and reduces the tone of the muscles. The rest of the pathologies were treated with various drugs such as Steroids, Gabapentin, Analgesics and Methycobal depending upon the existing musculoskeletal disorders. The various musculoskeletal cases treated included lumbosacral strain, cervical strain, frozen shoulder, intervertebral disc prolapse, muscle strain, radiculopathy, polyarthralgia, rheumatoid arthritis, stiff knee, post-gout stiffness, post-traumatic joint stiffness, ankylosing spondylitis and tennis elbow, etc.

After 5 to 10 days of treatment with Tolperisone, patients were evaluated clinically (for example, the straight leg raising test became negative, pain decreased and spasms related to disc prolapse reduced), and the severity of signs and symptoms were recorded. The self-administered questionnaire was given for recording subjective responses. In a questionnaire, questions are categorized into three parts.

Part A consists of demographic details like age, sex and socioeconomic status including occupation. Part B comprised questions related to relief from the signs and

symptoms and effects of the drug including a visual analog scale while part C had adverse effect-related questions.

#### Inclusion criteria

- ✓ Patients with musculoskeletal disorders with muscular spasms or spasticity and hypertonia.
- ✓ Male and female patients between the age group of 21-65 years.
- ✓ Non-hospitalized and non-ICCU patients.

#### Exclusion criteria

- ✓ Patients below 21 years and above 65 years of age.
- ✓ Hospitalized or patients in intensive care unit.
- ✓ Patients with cardiovascular (excluding hypertensive) and respiratory comorbidity.
- ✓ Pregnant females.
- ✓ Lactating mothers.
- ✓ Patients with renal and hepatic diseases.

**Ethical Approval-** Approval for this study was obtained from the relevant ethical committee, ensuring that all research procedures adhered to ethical standards and

guidelines for protecting participants' rights and confidentiality.

#### RESULTS

A total of 299 patients participated in the study including 194 males (65%) and 105 (35%) females. 264 (88%) cases were from urban backgrounds while 35 (12%) were from rural backgrounds. Most of the cases were of lumbosacral strain (52- 17.39%) followed by cervical strain (39- 13.04%), Frozen shoulder (38- 12.71%) and Lumbar vertebral disc prolapse (PIVD; 38- 12.71%) (Table 1).

In most of the cases, significant improvement was observed from the muscular spasm/stiffness etc as the

signs and symptoms reduced significantly. In the case of lumbosacral strain, 80% of 100% relief from the pain was observed as indicated by the visual analogue scale and results of questionnaire indicated. Moreover, the straight leg raising test became negative and muscular spasm reduced significantly (Table 1). The treatment with Tolperisone was uneventful except in one case where the patient reported a metallic taste.

**Table 1:** Diagnosed cases in the study

Diagnosis	Number of cases	Percentage (%)	Results	Adverse effects
Lumbosacral strain	52	17.39	80 to 100% relief from pain	Nil
Cervical strain	39	13.04	100% relief from pain and spasm	Nil
Frozen shoulder	38	12.71	Range of movements increased; Pain reduced	Nil
Lumbar vertebral disc prolapses (PIVD)	38	12.71	Pain and spasm reduced and straight leg raising test became negative	Nil
Lumber canal stenosis	22	7.36	Pain and spasm reduced	Nil
Lumber radiculopathy	17	5.69	Pain and spasm reduced and straight leg raising test became negative	Nil
Cervical radiculopathy	13	4.35	Pain and spasm reduced	Nil
Myalgia	9	3.01	Pain and spasm reduced	Nil

Hamstring strain	8	2.67	Pain and spasm reduced and movement freed	Nil
Sacroiliitis	8	2.67	Early morning stiffness reduced	Nil
Osteoarthritis knee joint	6	2.01	Range of movements increased and pain and stiffness reduced	Nil
Periscapsulitis	6	2.01	Pain reduced	Nil
Polyarthralgia	5	1.67	Early morning stiffness reduced	Nil
Postcolles fracture stiff wrist	5	1.67	Range of movements increased and pain and stiffness reduced	Nil
Rheumatoid arthritis	3	1	Early morning stiffness reduced	Nil
Hemiplegia	3	1	Stiffness reduced	Nil
Stiff knee	3	1	Range of movements increased and pain and stiffness reduced	Nil
Post traumatic elbow stiffness	3	1	Range of movements increased and pain reduced	Nil
Shoulder impingement syndrome	2	0.67	Pain reduced	Nil
Quadripareisis	2	0.67	Stiffness reduced	Nil
Contusion chest	2	0.67	Symptomatic pain and spasm reduced	Nil
Synovitis knee	2	0.67	Early morning stiffness reduced	Nil
Fracture volar barton	1	0.33	Stiffness reduced	Nil
Coccygodynia	1	0.33	Pain and stiffness reduced	Metallic taste
Fracture radius and ulna	1	0.33	Stiffness reduced	Nil
Multiple vertebral compression fracture	1	0.33	Pain and muscular spasm reduced	Nil
Post fracture calcaneus ankle stiffness	1	0.33	Pain and stiffness reduced	Nil
Avascular necrosis of hip joint	1	0.33	Stiffness reduced	Nil
Post gout stiffness	1	0.33	Stiffness reduced	Nil
Post-operative stiffness knee	1	0.33	Range of movements increased and pain reduced	Nil
Post traumatic knee joint stiffness	1	0.33	Range of movements increased and pain reduced	Nil
Post pott's fracture ankle stiffness	1	0.33	Pain and stiffness reduced	Nil
Pott's spine	1	0.33	Pain and muscle spasm reduced	Nil
Stiff wrist (post fracture)	1	0.33	Pain and stiffness reduced	Nil
Tennis elbow	1	0.33	Pain and spasm reduced	Nil

## DISCUSSION

Muscle relaxants are a group of drugs that are used to obtain reversible skeletal muscle relaxation. Depending on the site of action skeletal muscle relaxants are divided into two categories i.e. centrally acting and peripherally acting muscle relaxants according to their site of action. Centrally-acting drugs act on upper motor neurons while peripherally-acting drugs act on peripheral musculoskeletal elements.<sup>[4]</sup>

Tolperisone, which is a piperidine derivative belongs to a centrally acting group of skeletal muscle relaxants and has been in clinical use since 1960. The physicians recommend this drug for the treatment of muscle spasm and spasticity caused by various neurological disorders (e.g. cerebral palsy, traumatic brain injury, stroke, multiple sclerosis and different forms of spinal cord injury), traumatic neurological disorders, locomotor diseases (e.g. spondylarthrosis, arthrosis of large joints, low back pain, spondylosis, cervical and lumbar syndromes), vascular diseases (e.g. acrocyanosis, dysplasia angioneurotica intermittents), rheumatological diseases and rehabilitation following surgery in European Union countries.<sup>[10-13]</sup>

Stamenova *et al.*<sup>[8]</sup> conducted placebo-controlled randomized clinical trials on 120 patients of age group 18-75 years with central muscular spasticity. They used titrated doses of Tolperisone from 50 mg to 900 mg over 12 weeks. They observed clinical superiority over placebo with the use of Tolperisone more commonly in the daily dose of 600 mg in decreasing the post-stroke spasticity.

Melka *et al.*<sup>[5]</sup> conducted clinical trials in 72 patients having spasticity produced by neurolathyrism. It was a 12-week study with 300 mg of Tolperisone in two divided doses. After 12 weeks of treatment, they observed a significant decrease in spastic muscle tone in the adductors and Achilles in the Tolperisone treatment group in comparison to a placebo group.

Rao *et al.*<sup>[14]</sup> conducted a multicentric, randomized, comparative clinical trial in which they observed the efficacy and tolerability of Tolperisone by using 150 mg Tolperisone thrice a day or 8 mg Thiocolchicoside twice a day for 7 days during the treatment of acute low back pain with spasm of spinal muscles. The assessment was carried out by using a visual analogue scale, modified Schober's test finger to floor distance (FFD) and articular excursion in degrees by performing Lasegue's maneuver.

They observed a significant increase in articular excursion on Lasegue's maneuver and a significant decrease in FFD score from 3 to 7 days by using Tolperisone in comparison to Thiocolchicoside. However, they failed to observe significant variations in the increase of Schober's test score after using both drugs. In the conclusion, they mentioned that Tolperisone is an effectual and legitimate drug for the treatment of patients with skeletal muscle spasms associated with pain.<sup>[14]</sup>

Bajaj *et al.*<sup>[15]</sup> conducted a crossover study on Tolperisone to observe its prophylactic use in the management of post-exercise muscle sourness. Twenty male volunteers were involved in the study. They were given 150 mg of Tolperisone three times a day or placebo for 8 days. Pressure pain threshold was used as a parameter for assessment, Likert's pain score (0-5), pain areas, range of abduction, isometric force, electromyography (EMG) and root mean square (RMS) during maximum voluntary isometric force on day 1 and 6. Pain due to post-exercise muscle soreness is not relieved by prophylactic intake of Tolperisone hydrochloride but it leads to reduction in isometric force.<sup>[15]</sup>

Khan and Praveen<sup>[16]</sup> compared the effect of Tolperisone hydrochloride in 50 mg dose thrice a day with Tizanidine 2 mg thrice a day by using a Roland Morris questionnaire study on low back pain and disability in the patients of low back pain with muscle spasm to compare the efficiency and safety of the drugs. They observed statistically no significant difference among the groups for restrictions of movements, pain at night, pain at rest, changes in numbness, changes in stiffness, and changes in tenderness but observed a significant effect of Tolperisone for pain on movement and kinesia. Hence, they concluded that Tolperisone is comparable to Tizanidine during the management of acute low back pain with muscle spasms.

The exact mechanism of action of Tolperisone is unknown even though it has an inhibitory action on pathways of spinal reflexes. Through pre-synaptic and post-synaptic mechanisms, it suppresses the mono and polysynaptic reflex transmission. Tolperisone also reduces the reticulospinal facilitation in the brainstem. Due imbalance between the supraspinal facilitatory and inhibitory system leads to an increase in the reflex activity and an increase in muscle tone. Tolperisone also

suppresses the amplitude and frequency of action potentials and stabilizes the neuronal membranes leading to decreased pain. Tolperisone has a membrane stabilizing effect as its structure is similar to Lidocaine but Tolperisone predominantly acts on use-independent sodium channels connected to pain hence producing the most prominent effect in pain mechanism and thus showing a difference with Lidocaine. Moreover, pain-sensitive areas of the brain such as the prefrontal cortex, insula, thalamus and secondary somatosensory cortex are predominantly affected by Tolperisone. It acts on voltage-dependent calcium channels (N-type calcium channel blocking activity), blocks the voltage-gated sodium channels (reduction in sodium influx) reduces the transmitter release and produces inhibitory effects.

[10,13,17]

Hinck and Koppenhofer observed the effects of ionic currents on the node of Ranvier of sciatic nerves produced by Tolperisone. They observed the depression of the voltage-dependent current in the sodium channels with a concentration of 100  $\mu\text{mole/L}$ . [18] Quasthoff *et al.* [19] studied the blockage of the corresponding sodium currents by Tolperisone and reached an inference that Tolperisone directly blocks the voltage-dependent sodium channels. Kocsis *et al.* [20] in their study on dorsal root ganglia of rat pups, found that there is a shift in the position of steady state availability curve of voltage-dependent sodium current towards the negative potential with increasing Tolperisone concentration. They found that it also directly inhibits  $\text{Ca}^{2+}$  currents in the dorsal root ganglia. Quasthoff *et al.* [21] observed that Tolperisone blocks the small neuron  $\text{Ca}^{2+}$  currents in a frequency-dependent manner. They also observed that Tolperisone causes a shift of steady state availability of  $\text{Ca}^{2+}$  channels towards negative potentials. The above studies indicate that Tolperisone has antagonistic actions on both the  $\text{Na}^+$  channels and  $\text{Ca}^{2+}$  channels. A higher concentration of tolperisone is required for antagonistic action on  $\text{Ca}^{2+}$  channels as compared to  $\text{Na}^+$  channels. No adverse event was reported in the present study except in one case where a patient complained of a metallic test. Tolperisone is a well-tolerated, non-sedative drug with few side effects although some adverse effects were observed in various studies which include dizziness, fatigue, generalized body weakness and muscle pain which were not serious and did not require discontinuation of the drug treatment. A more

serious anaphylactic reaction was also observed with the use of Tolperisone. The range of grimness of anaphylaxis can vary from reactions due to urticaria to shock along with arterial hypertension. The above reports suggest that anaphylaxis reactions of Tolperisone are common.

[4,5,22,23]

Dulin *et al.* [24] observed the sedative effects of Tolperisone in 72 young healthy adults after giving single and repeated doses of 50 mg and 150 mg. The individuals received the doses three times a day for 8 days. The outcome was assessed using a battery of psychomotoric tests. The conclusion was that Tolperisone, even being a centrally acting muscle relaxant, neither causes any sedation nor impairs reaction times.

## CONCLUSIONS

The study concluded that Tolperisone at the dose of 150 mg is a good and safe muscle relaxant for various musculoskeletal disorders. It can be used to manage muscular spasms and stiffness in the cases of various musculoskeletal disorders without the sedative properties of various other drugs.

## CONTRIBUTION OF AUTHORS

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