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Original Research Article

Evaluation of efficacy and tolerability of eperisone and thiocolchicoside in treatment of low back pain associated with muscle spasm: An open label, prospective, randomized controlled trial

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ABSTRACT

Background: Low back pain has a high prevalence in adult population. Because of reflex muscle spasm, muscle relaxants are frequently used either alone or in combination with analgesics. Eperisone inhibits voltage gated sodium channels in brain stem and Thiocolchicoside acts via GABA-mediated mechanism to relax muscle spasm and relieves pain.
Methods: This was a prospective; open labeled, randomized, two-arm, parallel group, controlled, clinical trial. 113 patients were randomised to two groups. Patients in group A received Tablet Eperisone 100 mg whereas patients in group B received Tablet Thiocolchicoside 8 mg for seven days along with Tablet Paracetamol 500 mg. The outcome measures of trial were the improvement in finger to floor distance (FFD) and pain in lumbar region, relief of spasm and tenderness of paravertebral muscles on day 4 and 7.
Results: At the end of the study FFD reduced by 18 cm in group A ($p < 0.0001$*) and 17.36 cm in group B ($p<0.0001$*) from baseline. Mean score of pain on day 7 reduced by 5.64 scale in group A as compared to 5.42 scale in group B ($p<0.0001$* in both groups). Paravertebral tenderness reduced by 92.6% in group A and 94.6% in group B at the end of the trial. On day 7, the spasm relief was 87% in group A and 88% in group B.
Conclusions: Eperisone is an effective muscle relaxant with equivalent efficacy compared to Thiocolchicoside, and has a better tolerability in treatment of low back pain with muscle spasm.

Keywords: Eperisone, Low back pain, Thiocolchicoside

INTRODUCTION

Muscle spasm is sustained and painful involuntary contraction.[1] Musculoskeletal diseases associated with painful muscle spasm particularly low back pain has a high prevalence.[2] Low back pain is considered to be the result of a self-perpetuating cycle of pain and spasm.[2, 3] It has annual incidence of 10-15% and a point prevalence of 15-30% in adult population.[4] Low back pain is the most common cause of activity limitation in people younger than 45 years and second most common symptom related reason for visits to a physician.[5] The involvement of reflex muscle spasms leads to the frequent use of muscle relaxants, either alone or in combination with analgesics.[6] Muscle relaxants and non-steroidal anti-inflammatory drugs (NSAID) both categories have therapeutic utility in management of painful muscle spasms.[7] Development of sedation seems to be the limiting factor in the use of muscle relaxants for treatment, as they can affect daily activity and decrease working capability.[8,9] When voltage-gated sodium channels (VGSC) are blocked, it results in inhibition of neural activity and pain sensation. So VGSC remain viable targets for the development of novel analgesics.[10] Eperisone is a centrally acting muscle

relaxant that inhibits VGSC in the brain stem.[10,11] It inhibits mono and multi synaptic spinal reflexes.[11,12] Eperisone acts as an analgesic apart from being a muscle relaxant.[13] It is also considered to be less sedative muscle relaxant.[14,15] Thiocolchicoside (TCC) is a semi synthetic derivative from colchicoside. It acts via GABA-mediated mechanism to relax muscle spasm and relieve pain.[8] Hence this study was conducted to compare and evaluate the efficacy and tolerability of two non-sedative muscle relaxants, Eperisone and Thiocolchicoside in combination with Paracetamol, in patients suffering from painful muscle spasms associated with low back pain.

METHODS

This was a prospective, open labelled, randomized, two-arm, parallel group, controlled, clinical trial. It was conducted in compliance with the protocol, after Institutional Ethics Committee (IEC) approval, informed consent regulations, as per Declaration of Helsinki, ICH good Clinical Practice (GCP) guidelines and the ICMR guidelines for Biomedical Research on Human Subjects, 2006. Patients presenting with low back pain associated with skeletal muscle spasms attending the outpatient department (O.P.D.) of orthopaedics of a tertiary health care centre in Aurangabad from June 2013 to June 2014.

Patients of either gender between 18 to 55 years of age with acute musculoskeletal spasm associated with low back pain, as diagnosed by the orthopaedic surgeon, were included in the trial. All patients provided written, vernacular, witnessed, informed consent to participate in the trial. Patients with any abnormality other than the inclusion criteria seen by orthopaedic surgeon, patients treated with any other muscle relaxants, opioids, analgesics within one week prior to the trial or willing to continue to receive these drugs as concomitant medication during the trial period were excluded. Patients with known hypersensitivity to test or comparator medicine, history of significant hepatic, cardiac, renal and inflammatory bowel disease were excluded. Pregnant or lactating mothers were also not included in the trial.

Methodology

All patients willing to participate and give an informed consent were screened for eligibility. Baseline evaluation included recording of demographic details, medical history, general and systemic examination, and laboratory investigations, which included complete haemogram, hepatic and renal function tests and routine urine analysis.

The eligible patients were enrolled and randomized, by a computer generated randomization sequence, into two treatment groups. Patients in group A received Tablet Eperisone 100 mg thrice a day whereas patients in group B received Tablet Thiocolchicoside 8 mg twice a day for seven days. Patients in both the groups also received Tablet Paracetamol 500 mg thrice a day for seven days in addition to the trial medication. The patients were allowed to take Tablet Aceclofenac 100 mg as a rescue medication whenever the pain was unbearable. The patients were provided with diary and instructed to carefully record details of any adverse event or use of rescue medication. All patients were followed up for efficacy and safety assessment on day 4 and 7. (Fig 1)

The efficacy assessment included evaluation of severity of low back pain using FFD, paravertebral tenderness and visual analogue scale (VAS) for lumbar pain, and spasm. The safety was evaluated objectively by visual and auditory reaction time and sedation as measured on VAS. Any spontaneously reported adverse event was recorded in the standard format of ADR reporting. The FFD was evaluated by asking the patients to bend forward and try to touch the floor with fingers; the distance between fingers and ground (hand to floor) was measured by means of a ruler in centimetres. Improvement in lumbar pain was assessed on VAS (Score 0-10) with 0 representing 'no pain' and 10 representing 'severe intolerable pain'. Relief of spasm was assessed using VAS score (Score 0 – 10) as: 0 = no spasm relief, <4 = mild relief of spasm, 4.1- 7 = moderate relief of spasm, 7.1-9 = nearly complete relief of spasm, 9.1- 10 = complete spasm relief. Improvement in tenderness of paravertebral muscles was graded as, 0= no pain on firm pressure, 1 = slight pain on firm pressure, 2 = moderate pain on moderate pressure, 3 = severe pain on slight touch. The patients were explained the procedure of evaluation of safety parameters. Reaction time test was performed for assessing the auditory and visual response using reaction time apparatus. Sedation was calculated using a VAS (Score 0-10) on day 0 and 7 where 0 = no sedation, 1-3 = mild sedation, 4-7 = moderate sedation, and 8-10 = high sedation. Haematological and serological investigations were done before and after the trial.

Efficacy parameters

Primary outcome measure of the trial was the improvement in FFD from baseline on day 4 and 7 and secondary outcome measures were improvement in pain in lumbar region, relief of spasm and tenderness of paravertebral muscles.

Safety parameters

Visual and auditory reaction time and VAS score of the sedation were used as safety parameters.

Statistical analysis

All the data was entered into Microsoft Excel from case record form for analysis. For comparing quantitative data within the study groups Students Paired't' test and repeated measures ANOVA were used and for comparing quantitative data between the study groups Students Unpaired 't' test were applied. Comparison of qualitative data between the study groups was done using Fisher's

exact test. Statistical analysis was performed with the help of the software 'Graph pad Prism 5'. The p value of <0.05 was considered as statistically significant.

RESULTS

Total of 135 patients with acute low back pain were screened, and 113 eligible patients were randomized equally into two treatment groups. In group A 6 patients and in group B 7 patients were lost to trial. Both the groups were similar in demographic profile at baseline as shown in table 1. Both the groups showed significant reduction in all efficacy parameters (Table 2). FFD in group A reduced by 33.52% and 70.15% on day 4 and day 7 respectively while in group B it reduced to 35.21% on day 4 and 69.51% on day 7. VAS score of pain on day 4 was decrease by 49% in group A and 47% in group B and on day 7 it was decrease by 87% and 85% in group A and B respectively. Paravertebral tenderness in group A reduced by 67% and 92.6% on day 4 and day 7 respectively while in group B it reduced to 69% on day 4 and 94.6% on day 7.

Table 1: Baseline characteristics in study groups.

Parameter		Group A (n=50) EPN + PCM	Group B (n=50) TCC + PCM	'P' value
Age in years		43.50± 7.35	45.32± 6.72	0.2038†
Gender	Men (n)	23	21	0.8405‡
	Women (n)	27	29	
Finger to Floor distance (cm)		25.66±2.27	24.88±2.53	0.3690†
VAS score of Pain		6.52± 0.83	6.38±1.02	0.5938†
Paravertebral Tenderness score		1.62±0.52	1.48±0.50	0.2160†

EPN: Eperisone, TCC: Thiocolchicoside, PCM: Paracetamol, SD: Standard deviation, VAS: Visual Analogue Scale, n: Numbers; Values: Mean ± SD (otherwise mentioned); *: Statistically significant, †: Using 2-tailed unpaired t-test, ‡: Using Fisher's exact test.

Table 2: Efficacy assessment.

No.	Parameter	Group A EPN + PCM (Mean ± SD)	Group B TCC + PCM (Mean ± SD)	P value inter group†
1	Mean FFD in centimeter			
	Day 0	25.66 ± 2.27	24.88 ± 2.53	0.3690
	Day 4	17.06 ± 1.98	16.12 ± 1.67	0.0704
	Day 7	07.66 ± 0.84	7.52 ± 0.75	0.3898
	P value intragroup§	< 0.0001*	< 0.0001*	
2	Mean Pain score on VAS			
	Day 0	6.52 ± 0.83	6.38 ± 1.02	0.5938
	Day 4	3.34 ± 1.01	3.42 ± 1.00	0.6960
	Day 7	0.88 ± 0.59	0.96 ± 0.56	0.7009
	P value intragroup§	< 0.0001*	< 0.0001*	
3	Mean Tenderness score			
	Day 0	1.62 ± 0.52	1.48 ± 0.50	0.2160
	Day 4	0.54 ± 0.50	0.46 ± 0.50	0.5723
	Day 7	0.12 ± 0.32	0.08 ± 0.27	0.8452
	P value intragroup§	< 0.0001*	< 0.0001*	
4	Mean Spasm relief on VAS			
	Day 4	6.26 ± 0.59	6.34 ± 0.68	0.5812
	Day 7	8.82 ± 0.65	8.92 ± 0.82	0.5307
	P value intragroup§	< 0.0001*	< 0.0001*	

EPN: Eperisone, TCC: Thiocolchicoside, PCM: Paracetamol, SD: Standard deviation, VAS: Visual Analogue Scale, n: Numbers; Values: Mean ± SD (otherwise mentioned); *: Statistically significant, †: Using 2-tailed unpaired t-test, §: Repeated measure ANOVA.

None of the efficacy parameters showed any statistically significant difference between the two treatment groups at day 4 or 7 (Table 2). None of the safety parameters showed any statistically significant difference between the two treatment groups at baseline or day 7 (Table 3). Laboratory investigations did not show any significant change in both the groups before and after the completion of study. None of the patients required any rescue medication in either of the groups. Adverse effects were reported in six patients (12%) from group A as compared to12 patients (24%) from group B (Table 4). No serious ADRs were reported in any of the groups.

DISCUSSION

In most patients, low back pain is nonspecific and cannot be reliably attributed to a specific condition or abnormality in the back.[16] The goals of pharmacological intervention for acute low back pain is, not only the relief of pain, but also the reduction of muscle spasm and inflammation.[16,17] Muscle relaxants exert their pharmacological effects at the level of spinal cord, brainstem, cerebrum, and muscle fibre. Their centrally mediated mechanism of action can exert a clinically significant peripheral therapeutic effect.[18] The addition of a skeletal muscle relaxant to Paracetamol or other non-steroidal anti-inflammatory drugs (NSAID) may be more effective than the analgesic alone.[19,20]

Table 3: Safety assessment.

No.	Parameter	Group A EPN + PCM (Mean ± SD)	Group B TCC + PCM (Mean ± SD)	P value inter group†
1	Score of Visual reaction time			
	Day 0	0.778 ± 0.124	0.780 ± 0.124	0.9334
	Day 7	0.792 ± 0.124	0.794 ± 0.123	0.9892
	P value intragroup‖	0.2762	0.2774	
2	Score of Auditory reaction time			
	Day 0	0.726 ± 0.127	0.730 ± 0.124	0.9076
	Day 7	0.733 ± 0.108	0.741 ± 0.113	0.9661
	P value intragroup‖	0.2975	0.2850	
3	Score of sedation			
	Day 0	0.12 ± 0.325	0.14 ± 0.347	0.8769
	Day 7	0.10 ± 0.300	0.12 ± 0.325	0.9224
	P value intragroup‖	0.6219	0.6420	

EPN: Eperisone, TCC: Thiocolchicoside, PCM: Paracetamol, SD: Standard deviation, VAS: Visual Analogue Scale, n: Numbers; Values: Mean ± SD (otherwise mentioned); *: Statistically significant, †: Using 2-tailed unpaired t-test, §: Repeated measure ANOVA, ‖: paired t- test

Table 4: Adverse effects.

Type of adverse effect	Group A (EPN + PCM)	Group B (TCC + PCM)
Gastric complaints	3 (6%)	3 (6%)
Diarrhoea	0 (0%)	5 (10%)
Headache	2 (4%)	1 (2%)
Nausea	1 (2%)	1 (2%)

Eperisone is a muscle relaxant, with a mechanism of action slightly different from that of other muscle relaxants. In addition to inhibition of mono and multi synaptic reflexes in the spinal cord and supra-spinal structures, Eperisone regulates the blood supply to skeletal muscles.[11] This action is noteworthy since a muscle contracture may compress the small blood vessels and induce an ischemia leading to release of nociceptive compounds. More importantly, Eperisone is devoid of detrimental effects on the central nervous system. [11, 21] Thiocolchicoside and Eperisone are muscle relaxants which mediate muscle relaxation without concomitant sedation and withdrawal phenomenon. [1, 8]

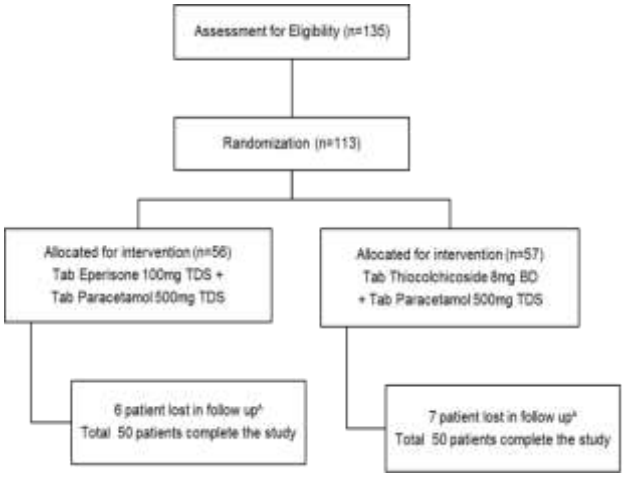

Figure 1: Flowchart showing the run–in of intervention.

In the study carried out by Cabitza et al[11] the FFD decreased from 20.31 cm to 13.86 cm with Eperisone ($p < 0.001$ vs. basal), and from 19.88 cm to 15.53 cm with Thiocolchicoside ($p < 0.001$ vs. basal). Similar results were obtained on day 7 in studies by Silvana et al[12] and Chandanwale et al[22] using Eperisone. Rao et al[23] and Soonawalla et al[24] demonstrated same results with Thiocolchicoside ($p<0.005$). In the study carried out by

Cabitza et al[11] the VAS score of pain decreased significantly in patients receiving Eperisone and Thiocolchicoside ($p < 0.001$ vs. basal in both groups). Frandisco et al[25] and Soonawalla et al[24] demonstrated a statistically significant decrease in muscle spasm with Eperisone 300mg and Thiocolchicoside 8mg respectively. In the study carried out by Cabitza et al[11] the pain on pressure was significantly improved in patient treated with Eperisone and Thiocolchicoside. Frandisco et al[25] and Ketenci et al[8] found that there was lack of significant effect on attention and cognitive function as well as on other normal daily life activities by using Eperisone and Thiocolchicoside respectively.

As a result of paravertebral muscle spasm the flexion of the vertebral column is restricted so FFD is considered to be an index of mobility. In our study Eperisone and Thiocolchicoside caused statistically significant reduction in FFD. At the end of the trial the FFD reduced by 18 cm in Eperisone group and 17.36 cm in Thiocolchicoside group from baseline. No significant difference was found in intergroup comparison. Mean VAS score of pain reduced significantly on day 7. Mean score of pain on VAS reduced by 5.64 scale in Eperisone group as compared to 5.42 scale in Thiocolchicoside group. There was statistically significant reduction in paravertebral muscle tenderness. On day 7, the spasm relief was 87% and 88% in Eperisone and Thiocolchicoside group respectively. In intergroup comparison the difference in VAS score of pain, paravertebral tenderness and spasm relief were not significant. There was no significant increase in sedation, visual as well as auditory reaction times in both groups at the end of the study. The tolerability was better in Eperisone group (few gastrointestinal ADRs) as compared to Thiocolchicoside group.

CONCLUSION

Eperisone is an effective skeletal muscle relaxant with equivalent efficacy compared to Thiocolchicoside, and has better tolerability in the treatment of patients with low back pain associated with muscle spasm.

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