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RESEARCH ARTICLE

Efficacy of eperisone and tizanidine on visual and auditory reaction time: A prospective, double-blind randomized controlled trial

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ABSTRACT

Background: Musculoskeletal diseases with painful reflex muscle spasm have a high prevalence. 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 tizanidine acts on imidazoline and α2-adrenergic receptor to relax muscle spasm and relieves pain. The development of sedation seems to be the major limiting factor in the use of muscle relaxants for treatment as they can affect daily activity and decrease working capability. **Aims and Objectives:** The present trial conducted to evaluate the effect of eperisone and tizanidine on visual and auditory reaction time. **Materials and Methods:** This was a prospective, double-blind, parallel group, randomized clinical trial. A total of 115 patients were randomized into two groups. Patients in Group A received tablet eperisone 100 mg and patients in Group B received tablet tizanidine 2 mg for 7 days. Primary outcome measures were changed in visual and auditory reaction time from baseline to day 7. Secondary outcome measure of the trial was change in the visual analog scale (VAS) score of the sedation from baseline to day 7. **Results:** On day 7, the difference in visual reaction time in Group A and B was 0.014 and 0.077, respectively, and this difference is statistically significant ($P = 0.029$). Difference in Auditory reaction time on day 7 in Group A and B were 0.007 and 0.091, respectively, and it is statistically significant ($P = 0.004$). There was increase in sedation score in Group B by 0.34 and it is statistically significant ($P = 0.015$). **Conclusion:** Tizanidine increases visual and auditory reaction time and sedation which is not seen with eperisone. Eperisone is a preferred alternative for muscle relaxation to avoid these effects.

KEY WORDS: Muscle Spasm; Eperisone; Tizanidine

INTRODUCTION

Muscle spasm is a sustained involuntary contraction which is usually painful and cannot be completely relieved by voluntary effort.[1] Musculoskeletal diseases associated with painful reflex muscle spasm have a high prevalence in the general population.[2] Musculoskeletal disorders have been among the most commonly reported work-related illnesses.[3] About 50% of people with muscle spasm experience muscle spasm-related pain or discomfort.[2] Muscle spasm may occur in almost any muscle. Spasms often having reflex origin, due to peripheral irritation affecting muscles or nerves or result from central processes. Muscle spasms also caused by the limitation of articular function resulting from inflammatory or degenerative arthropathies.[4] During spasm, the blood vessels that feed the muscles and supply oxygen constrict, which further compounding the problem.[4,5] Pain is a common cause of defensive spasm and reflex rigidity.[4]

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The involvement of reflex muscle spasms resulting in a "pain-spasm-pain" cycle leads to the frequent use of muscle relaxants either alone or in combination with analgesics.[6] The action of eperisone as centrally acting muscle relaxant is principally based on the inhibition of voltage-gated sodium channels in the brain stem.[7,8] It inhibits mono- and multi-synaptic spinal reflexes and also increases blood flow to skeletal muscles.[8,9] Tizanidine is another muscle relaxant acts on imidazoline and α2-adrenergic receptor. Tizanidine has both spinal and supraspinal sites of action.[10-12]

The centrally active muscle relaxants have considerable side effects such as sedation, dizziness, impairment of coordination, mental confusion, weakness, withdrawal phenomenon, or anticholinergic adverse events. These common side effects often impair the cooperation of the patients with therapy and their ability to work.[1,13] The development of sedation seems to be the major limiting factor in the use of muscle relaxants for treatment as they can affect daily activity and decrease working capability.[13,14] Hence, the present trial conducted to evaluate the effect of eperisone and tizanidine on visual and auditory reaction time.

MATERIALS AND METHODS

This was a prospective, double-blind, two-arm, parallel group, randomized clinical trial.The study protocol was approved by the Institutional Ethics Committee and conformed to the principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and Indian Council of Medical Research Guidelines for Biomedical Research on Human Subjects, 2006. Patients presenting with pain associated with skeletal muscle spasms attending the outpatient Department of Orthopaedics of a tertiary health-care center in Aurangabad from June 2013 to June 2014 were recruited in trial.

Patients of either gender between 18 and 55 years of age with acute musculoskeletal spasm associated with pain, as diagnosed by the orthopedic 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 orthopedic surgeon, patients treated with any other muscle relaxants, opioids, central nervous system (CNS) depressants drugs, analgesics within 1 week before the trial or willing to continue to receive these drugs as concomitant medication during the trial period were excluded from the study. 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. 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 tizanidine 2 mg thrice a day for 7 days (Figure 1).

To evaluate reaction time test for auditory and visual responses reaction time apparatus was used. The subjects were explained about the test - a brief training for awareness was given to every subject. Subjects have to respond by pressing the respective button on receiving the stimulus. Procedure - the apparatus had 2 components - examiners component (A) and subject component (B). These 2 components were separated by an opaque sheet. The subjects' component had a display of 3 colored lights - red, green, and yellow and a buzzer that played 3 different kinds of sounds. There were also 3 buttons of red, green, and yellow colors and 3 buttons named 1, 2, and 3 to be responded to the respective stimuli (Figure 3). The examiners component had buttons to produce these above-mentioned stimuli and a screen that displayed the reaction time in seconds (Figure 2).

Sedation was calculated using a visual analog scale (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.

- Primary outcome measures were change in visual and auditory reaction time from baseline to day 7.
- Secondary outcome measure of the trial was change in the VAS score of the sedation from baseline to day 7.

Statistical Analysis

All the data were entered into Microsoft Excel from case record form for analysis. For comparing quantitative data within the study groups, Students' paired *t*-test was used and for comparing quantitative data between the study groups, Students' unpaired *t*-test was 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 $P < 0.05$ was considered statistically significant.

RESULTS

A total of 141 patients with muscle spasm associated with pain were screened, and 115 eligible patients were randomized into two groups. A total of 6 patients in Group A and 9 patients in Group B were lost to trial. Both groups were similar in demographic profile at baseline as shown in Table 1. On day 7, the difference in visual reaction time in Group A and B was 0.014 and 0.077, respectively, and this difference is statistically significant ($P = 0.029$). Difference

in auditory reaction time on day 7 in Group A and B was 0.007 and 0.091, respectively (Table 2), and it is statistically significant ($P = 0.004$). There was increase in sedation score in Group B by 0.34 (Table 2) and it is statistically significant ($P = 0.015$).

DISCUSSION

Muscle spasm is a symptom of many muscular and other types of disorders. It produces muscular rigidity and acts as a protective mechanism to prevent movement and further damage of the affected part. Muscle spasm, however, is one of the principal factors related to the persistence of the pain.[13,15] The goals of treatment not only the relief of pain but also the reduction of muscle spasm and inflammation.[16,17] Muscle relaxants exert their effects at the level of spinal cord, brainstem, cerebrum, and muscle fiber. 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 may be more effective than the analgesic alone.[19,20]

Table 1: Baseline characteristics in the study groups (n=50 in each group)

Parameter	Group A (eperisone)	Group B (tizanidine)	*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	
Visual reaction time	0.778±0.124	0.764±0.103	0.551†
Auditory reaction time	0.726±0.127	0.711±0.111	0.535†
VAS score of sedation	0.12±0.325	0.08±0.271	0.510†

Values are represented in Mean±SD (otherwise mentioned).
SD: Standard deviation, *n*: Numbers; VAS: Visual analog scale, *Statistically significant, †Using two-tailed unpaired *t*-test, ‡Using Fisher's exact test

Table 2: Comparison of outcome measures in Group A and Group B

Parameter	Group A (eperisone)	Group B (tizanidine)	*P* value inter group†
Score of visual reaction time			
Day 0	0.778±0.124	0.764±0.103	0.551
Day 7	0.792±0.124	0.841±0.094	0.029*
P value intragroup‖	0.2762	<0.001*	
Score of auditory reaction time			
Day 0	0.726±0.127	0.711±0.111	0.535
Day 7	0.733±0.108	0.802±0.119	0.004*
P value intragroup‖	0.2975	<0.001*	
Score of sedation			
Day 0	0.12±0.325	0.08±0.271	0.510
Day 7	0.10±0.300	0.42±0.851	0.015*
P value intragroup‖	0.6219	0.001*	

Values are represented in mean±SD (otherwise mentioned).
SD: Standard deviation, *n*: Numbers, VAS: Visual analog scale, *Statistically significant, †Using two-tailed unpaired *t*-test, ‖Using Fisher's exact test

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 supraspinal structures, eperisone regulates the blood supply to skeletal muscles.[8] 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 CNS.[8,21] Eperisone is a muscle relaxants which mediate muscle relaxation without concomitant sedation and withdrawal phenomenon.[1,13]

Tizanidine acts on imidazoline and α2-adrenergic receptor. Tizanidine has both spinal and supraspinal sites of action.[10-12] Action of tizanidine on imidazoline receptors is involved in the supraspinal inhibitory effects on spinal reflexes, and at the spinal level, α2-adrenoceptors and imidazoline receptors are involved in the inhibitory effects.[22,23] Tizanidine binds to α2A and α2C adrenergic receptor and the increased inhibition of neurotransmitter release. All these effects produce muscle relaxation as well as sedation.[10-12]

In this trial, there was a significant increase in both visual and auditory reaction times in the tizanidine group whereas no increase in the eperisone group. This finding is in accordance with the study carried out by Dulin et al.[24] and Farkas et al.[25] and Cabitza and Randelli.[8] There was a significant increase in sedation in the tizanidine group on day 7. No such change in sedation seen in the eperisone group. This result is in accordance with the studies by Ketenci et al.,[13] Dulin et al.,[24] Farkas et al.,[25] Cabitza and Randelli.,[8] and Berry et al.[26]

CONCLUSION

Tizanidine increases visual and auditory reaction time and sedation which is not seen with eperisone. Eperisone is a preferred alternative for muscle relaxation to avoid these effects.

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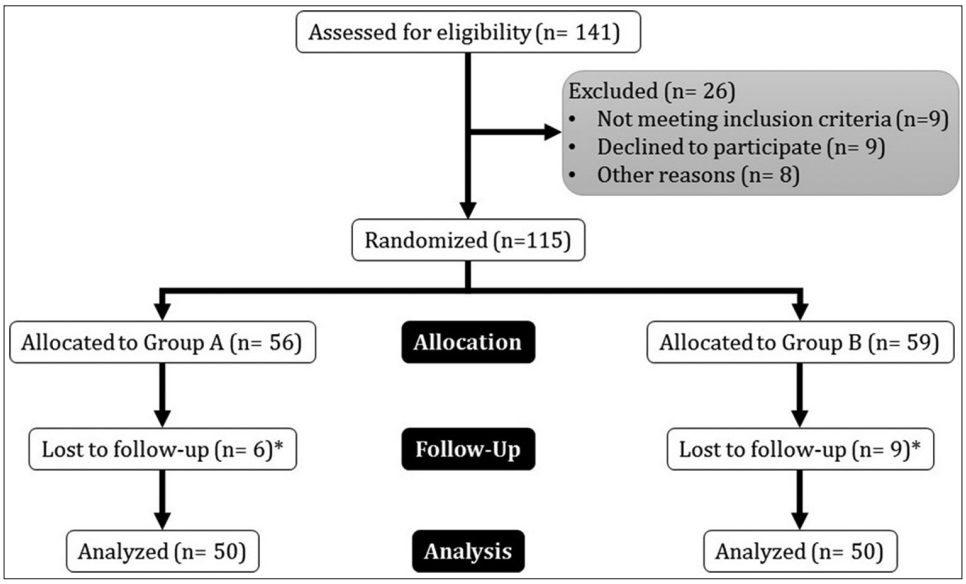

Figure 1: Flowchart showing the run-in of intervention. *These patients were lost to trial because of abnormal laboratory parameters or when some patients started taking concurrent medications or patients from remote area who did not report for follow-up

Figure 2: Reaction time apparatus showing examiners component

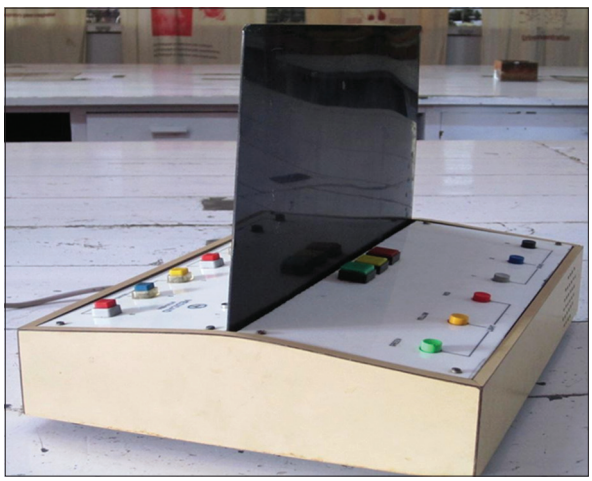

Figure 3: Reaction time apparatus showing subject component

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