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European Journal of Pain 7 (2003) 407–418
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Prophylactic tolperisone for post-exercise muscle soreness causes reduced isometric force – a double-blind randomized crossover control study

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Received 10 July 2002; accepted 10 December 2002

Abstract

The role of tolperisone hydrochloride, a centrally acting muscle relaxant in relieving painful muscle spasm is recently being discussed. The present study hypothesizes that the prophylactic use of tolperisone hydrochloride may effectively relieve post-exercise muscle soreness, based on the spasm theory of exercise pain. Twenty male volunteers, aged 25.2 ± 0.82 years (mean $\pm$ SEM) participated in 10 sessions in which they received oral treatment with placebo or the centrally acting muscle relaxant tolperisone hydrochloride (150 mg) three times daily for 8 days, in randomized crossover double-blind design. Time course assessments were made for pressure pain threshold, Likert's pain score (0–5), pain areas, range of abduction, isometric force, and electromyography (EMG) root mean square (RMS) during maximum voluntary isometric force on day 1 and 6, immediately after an eccentric exercise of first dorsal interosseous muscle, and 24 and 48 h after the exercise. Treatment with placebo or tolperisone hydrochloride was initiated immediately after the assessments on the first day baseline assessments. On the sixth day baseline investigations were repeated and then the subjects performed six bouts of standardized intense eccentric exercise of first dorsal interosseous muscle for provocation of post-exercise muscle soreness (PEMS). Perceived intensity of warmth, tiredness, soreness and pain during the exercise bouts were recorded on a 10 cm visual analogue pain scale. VAS scores and pressure pain thresholds did not differ between tolperisone and placebo treatment. All VAS scores increased during the exercise bouts 2, 3, 4, 5 and 6 as compared to bout 1. Increased pain scores and pain areas were reported immediately after, 24 and 48 h after exercise. Pressure pain thresholds were reduced at 24 and 48 h after the exercise in the exercised hand. Range of abduction of the index finger was reduced immediately after the exercise and was still reduced at 24 h as compared to the non-exercised hand. The EMG RMS amplitude was also reduced immediately after the exercise, but was increased at 24 and 48 h. Isometric force was reduced immediately after the exercise as compared to days 1, 6, and the 24 and 48 h post-exercise assessments with a greater reduction following the tolperisone hydrochloride treatment and the reduction was more in tolperisone group as compared to the placebo group. The results suggest, that the prophylactic intake of tolperisone hydrochloride provides no relief to pain in course of post-exercise muscle soreness but results in reduction in isometric force.

Keywords: Central muscle relaxant; Randomized clinical trial; Post-exercise muscle soreness; Experimental muscle pain; Isometric force; EMG

1. Introduction

Muscular pains are the most common source of pain encountered in humans (Brattberg et al., 1989), and often tend to become chronic, therefore early treatment and pain management are essential. Intense eccentric exercise is followed by post-exercise muscle soreness (PEMS) and muscle weakness that may mimic the pain and weakness of muscle-damage in disease (Abraham, 1977). Early studies showed that electromyography (EMG) root mean squared amplitude (RMS) increased after the exercise induced muscle pain and these changes reverse on giving stretching treatment (de Vries, 1960,

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1090-3801/$30
doi:10.1016/S1090-3801(02)00145-3

1962, 1966). On this basis it was suggested that muscle spasm is mainly responsible for pain, and the theory became popularly known as the spasm pain theory (de Vries, 1960, 1962, 1966). Further EMG studies did not confirm the findings of spasm related pain (Abraham, 1977; Bajaj et al., 2001d; Chleboun et al., 1998; Howell et al., 1985, 1993; Jones et al., 1987; Newham et al., 1983). If muscle spasm were to be essential for development and maintenance of PEMS, then muscle relaxants should be effective to prevent or alleviate the symptoms. In addition, the indiscriminate use of non-steroidal inflammatory drugs (NSAIDs) in sports and occupational medicine has been shown to have long-term detrimental effects including myofibrillar protein loss and force deficit at 3 days after muscle damage, which was still apparent at 28 days (Mishra et al., 1995). However, animal studies have shown histological evidence of protective effects of NSAID Indomethacin (Salminen and Kihlstrom, 1987) and prednisolone (Kihlstrom et al., 1984) in exercise induced injuries and inflammation. But, aspirin produced little or no effect at doses of 1200–2400 mg/day and was shown to lower PEMS 48 h after exercise in a considerably higher dose (3000 mg/day) (Francis and Hoobler, 1987). NSAID Flurbiprofen failed to shown any relief in muscle soreness in man (Kuipers et al., 1985). In another study, NSAID diclofenac administered orally from pre-exercise to 72 h in humans fail to show analgesic effects after down hill eccentric exercise muscle damage (Donnelly et al., 1988). Donnelly et al. (1990) also found Ibuprofen to be ineffective in post-exercise muscle soreness.

Tolperisone hydrochloride is a centrally acting muscle relaxant (Perenyi, 1978) that is non-sedative and does not impair reaction times (Dulin et al., 1998). In this study a battery of psychomotoric tests and mood ratings showed that tolperisone in doses of 50 and 150 mg trice daily for 8 days has no sedative effects (Dulin et al., 1998). The sedative effects were present in 0.8% in Dulin et al. (1998) study, which was far below the incidence reported on placebo in controlled trials with other muscle-relaxing drugs (Dapas et al., 1985; Smith et al., 1994; Wallace, 1994). In rat experiments, tolperisone did not potentiate the effects of alcohol with respect to alcohol induced sleep or craving for alcohol (Dulin et al., 1998).

Tolperisone has a membrane stabilizing effect, and it reduces the sodium influx through isolated nerve membranes (Farkas et al., 1997; Fels, 1996). It has been shown that tolperisone acts as an adjuvant to the anti-inflammatory agents to reduce pain in the locomotor disease patients (Galos, 1992). Tolperisone has also been shown to act as an adjuvant to physiotherapy in relieving pain due to muscular hypertonia (Kiss and Martos, 1993). Significant reduction in spasticity due to motor neuron disease in patients suffering from neurolathyrism is also reported (Haque et al., 1994). In the same disease Melka et al. (1997) could also demonstrate significant improvement in subjective complaints such as muscle cramps, heaviness of the legs, startle attacks, flexor spasms and repeated falls in neurolathyrism. Oral tolperisone hydrochloride significantly reduced muscular aching and vascular flushing complaints in menopausal women not responding to oestrogen substitution therapy (Sasdi, 1992).

Beneficial effects of tolperisone in painful reflex muscle spasm could also be demonstrated in a randomized, double-blind, placebo controlled clinical trial. Tolperisone significantly increased the pressure pain threshold compared with placebo (Pratzel et al., 1996). On the basis of these results it can be suggested that tolperisone hydrochloride is an effective muscle relaxant that does not cause any sedation. Considering the role of tolperisone in relieving painful muscle spasm and based on the spasm theory of exercise pain (de Vries, 1960, 1962, 1966) we hypothesized that it may effectively relieve post-exercise muscle soreness. PEMS is also associated with the development of peripheral sensitization and subsequent muscle stretching of daily activities or muscle spasm may serve to maintain the central sensitization initiated at the onset (Bajaj et al., 2000, 2001a,d). The aim of the study was to use a double-blind randomized placebo controlled crossover design to study the prophylactic effect of tolperisone towards PEMS of the first dorsal interosseous muscle of the hand (FDI), regarding pain and muscle contraction force.

2. Material and methods

2.1. Subjects

Twenty healthy male volunteers (16 right handed and 4 left handed), aged 25.2 ± 0.82 years; height 182 ± 1.7 cm; and weight 80.9 ± 2.7 kg (mean $\pm$ SEM) were studied over a period of 8 days and participated in a total of 10 sessions. All the subjects signed an informed consent and the study was conducted according to the declaration of Helsinki and approved by the local ethics committee. Subjects having positive histories of medical illnesses and intake of any medication were excluded from the study.

2.2. Study medication

Oral tablets of 150 mg tolperisone hydrochloride or placebo (supplied by Strathmann AG, Germany) in a dose of one tablet thrice daily for 8 days were commenced prophylactically 6 days prior to the exercise bouts and were continued until the last experimental investigations were performed on the day 8. The placebo tablets were identical to the tolperisone hydrochloride in terms of their size, colour, shape and smell.

2.3. Randomization

The study was divided into two periods (1 and 2), which were separated by a 4 weeks wash out interval. During "period 1" the choice for the medication (A or B), exercise hand (left or right) was randomly divided between an equal number of subjects. The subjects picked up one folded paper slip from two boxes containing equal number of two types (10 each) of slips. One box contained slips for the type of tablets, with 'A' or 'B' written on them and the second box for the use of hand for the exercise, with 'right' or 'left' written on them. During "period 2" type of medication and exercise hand was reversed for all the subjects. The randomization slip were prepared by a technician not involved in the experiments and not known to the investigators. The randomization code table for the medication was prepared and kept by the drug company (Strathmann AG, Germany). After completion of the experimental part of the study the randomization code for the sequence of the different medications 'A' or 'B' for each subject was disclosed and when the statistical analysis was performed for all the parameters and the percentage changes occurring on days 6–8 were compared with day 1, i.e., before any exercise, placebo or tolperisone was undertaken, the actual placebo and true drug codes were disclosed.

2.4. Study procedures

The exercise apparatus used in the present study has been described in detail in our previous studies that assessed the functions of the first dorsal interosseous muscle of hand (Bajaj et al., 2000, 2001b,d). The exercise and assessment methods for the range of motion (abduction) of the index finger, the concentric maximum voluntary contraction (MVC), the maximum voluntary isometric force and the EMG RMS (mV), the pain assessment methods by pressure pain threshold, verbal Likert's pain score, visual analogue scale, and pain areas were demonstrated to the subjects, as described below. The assessment methods were again repeated before undertaking the exercise on day 6, immediately after the exercise, and on day 7 and day 8. A point corresponding to the centre of the first dorsal interosseous muscle of hand was marked with a non-toxic permanent ink as a landmark for soreness, and EMG assessments. This was the point of intersection of perpendicular lines drawn at the level of the junction of the proximal 1/3rd and the distal 2/3rd of the 1st and 2nd metacarpal bones.

2.5. Exercise apparatus and eccentric exercise

Briefly, the hand exerciser consisted of an adjustable height platform with an opening for flexing the 3rd, 4th and 5th fingers, and a custom-fitted splint for the index finger. Ball bearings were located underneath the splint to reduce surface friction. Weights were added to a non-extensible wire connected to the index splint (mean ± SEM) through a pulley. Another wire connected the same weights to a foot pedal through another pulley placed below the first one (Bajaj et al., 2000). The finger splint rotated around an axis positioned under the second metacarpophalangeal joint. An electronic potentiometer was used to record the range of motion. The subjects were seated on a comfortable chair with the right arm and forearm resting on a horizontal platform. The right arm was abducted at 90°, elbow was flexed at 90° and the hand was placed palm down. Velcro belts were tightened around the right forearm, the right wrist, and the right thumb. The right shoulder joint was stabilized with a vacuum pillow (Ambu, Kristianstad, Sweden). The index finger was at its neutral position in relation to the anatomical axis passing through the middle finger and was placed and strapped in a splint. The three last fingers were fully flexed in an opening to minimize co-contraction from the extensor muscles, palmar interossei and lumbrical muscles (Fig. 1A). The first dorsal interosseous muscle of the hand was first contracted by maximally abducting the index finger (concentric contraction) and the pedal was then pressed. The weights were then gradually added to increase the load until abduction angle decreased more than 5°, and this weight was recorded as the concentric MVC. Between each increment of weight the pedal was pressed for 10 s so as to avoid muscle fatigue. After the concentric MVC measurements, the subjects rested for 5 min. Measurements of the isometric MVC force and EMG were then recorded. In this experiment the subjects were instructed to abduct the index finger isometrically with their maximum force for 3 s against the pulley fixed to the force transducer mounted on a steel plate (Fig. 1).

After the baseline recordings, the subjects started the oral medication for eight days (one tablet thrice daily). On each subsequent visit, an adverse reaction report and details of intake of medications were recorded. On the sixth day subjects were again examined and all the parameters of day 1 were repeated. The subject then performed 6 bouts of eccentric exercise separated by a 2 min rest. Prior to the actual exercise procedure the subject practiced for 5 min the eccentric exercise at sub-maximum voluntary contraction load. A total of 115–120% MVC (measured on day 1) was then added to the pulley, while the subjects kept the pedal pressed to avoid load bearing on the index finger. The subjects then removed the foot from the pedal suddenly and provided their maximal voluntary resistance to hold the weights using the index finger muscles, as the finger approached the neutral position. The subjects pressed the pedal, took their finger back to a fully abducted position and restarted the eccentric contraction by releasing the pedal again. This

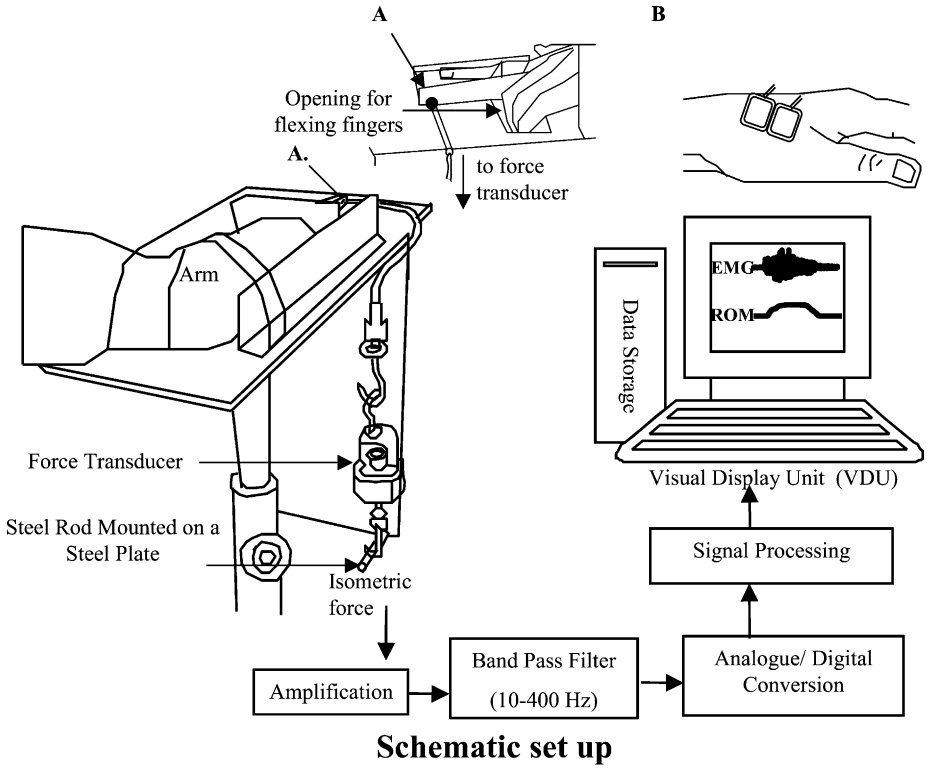

Fig. 1. Showing the hand exerciser being used for the assessment of isometric force and a schematic diagram for electronic data collection and storage. Inset (A) close-up view of the index splint. Inset (B) close-up view of placement of EMG surface electrodes on the first dorsal interosseous muscle and induction of post-exercise muscle soreness of the first dorsal interosseous muscle of hand.

process was continued for 2 min. The subjects rested for 2 min before starting the next bout of the exercise. Each of the subjects performed a total of six bouts of exercises. For those of the subjects who were unable to hold this weight in a fully abducted position, exercise was carried out with lesser weights. Immediately after the each bout of exercise, subjects reported the perceived intensity of tiredness, warmth and pain on a 0–10 cm visual analogue scale (VAS). At, immediately after, 24 h (day 7), and 48 h (day 8) after the exercise the subjects underwent all the assessments as were done on day 1 and 6.

2.6. Pressure pain thresholds (PPT)

The PPT can be used to evaluate the development and decline of experimentally induced muscle tenderness (Nussbaum and Downes, 1998). An automatic electronic pressure algometer (Noxitest Biomedical Engineering A/S Aalborg, Denmark) with a probe of 1 cm^2 diameter was used to measure PPT in kiloPascals (kPa). The probe was pressed at a point marked at the centre of the first dorsal interosseous muscle of hand. A constant rate of pressure increase (98.2 kPa/s) was applied until the subject pressed a button at a point where the pressure was first perceived as painful (PPT) and this froze the pressure application and the pressure probe returned to the start position. The PPT was displayed on the visual display unit. The use of this automated algometer avoids the error due to the fluctuation of the pressure rate by the examiner as seen for some hand held algometers.

2.7. Pain areas

The subjects were asked to locate the regions associated with pain after exercise and draw these on anatomical drawings. The drawings consisted of the anterior and posterior views and the palmar and dorsal surface of hands. The circumference of the drawing on the maps was digitized (ACECAD D9000 + digitizer, Taiwan), and the area calculated in arbitrary units (AU) (Sigma-Scan, Jandel Scientific, Canada). As the size of the pain drawing did not match the actual hand size, arbitrary units were used for the calculations of the pain areas. If the subject perceived no pain, the pain areas were included in the statistics as zero.

2.8. Range of motion

The maximum lateral angular displacement of the index finger (abduction) was measured with goniometer (Bajaj et al., 2001d; Madeleine et al., 2000), placed underneath the hand platform corresponding with the axis of the second metacarpal joint while the finger was positioned in the finger splint. The goniometer consisted of

a linear potentiometer, an amplifier and a display unit, i.e., a multimeter (Fluk, Tilburg, The Netherlands) and was sampled at 500 Hz.

2.9. Isometric force and surface EMG

For recording the isometric force, the finger splint was fixed to a steel rod via a force transducer (Entran, Herts, England) (Fig. 1B). The subjects were encouraged by 'cheering-up' to apply force at a constant speed against a constant resistance with no observable joint movement for 3 s. The force transducer was connected to a multimeter (Fluk, Tilburg, The Netherlands). Surface electromyography data were collected with the use of bipolar EMG surface electrodes (Neuroline 720-01-k, Ølstykke, Denmark) placed 20 mm apart on ethanol-cleaned and abraded skin over the first dorsal interosseous muscle of the hand (Fig. 1B). Pre-amplifiers with a gain of 100 were attached to the electrodes (Aalborg University, Denmark). A ground electrode soaked with saline was attached to the wrist. In total, the EMG signals were amplified 1000 times, band-pass filtered at 10–400 Hz, sampled at 1000 Hz and stored. On line calculation of the maximum force was performed. The RMS value was then computed over a 200 ms window starting 50 ms before the maximum force timing.

2.10. Statistical analysis

The data were tested using one-way, two-way or three-way repeated measure ANOVA (RMANOVA). Analyses of significant results were carried out using the Student–Newman–Keuls test for multiple comparisons. The factors in the ANOVA for intensive exercise measurements were medication (2 levels, tolperisone and placebo) and exercise bout (6 levels, bouts 1–6). The factors in the ANOVA for the range of motion, isometric force, values of EMG RMS, self-assessment Likert's scale (0–5), and pain areas were medication (2 levels, tolperisone and placebo) and day of the experiments (5 levels, day – 1, 6, immediately after, 7, and 8). The factors in the ANOVA for the PPT were medication (2 levels, tolperisone and placebo), hand (2 levels, exercised and non-exercised) and day of the experiments (5 levels, days 1, immediately after, 6–8). Correlation was carried out using Spearman's correlation analysis. Significance was accepted at $P \leqslant 0.05$. The data were expressed as means ± standard error of the mean (SEM).

3. Results

3.1. Perceived intensity of sensation during exercise

Warmth, tiredness, pain and soreness were the most common sensations felt during the intense eccentric exercise of FDI. Three-way RMANOVA analysis showed that the VAS score depended on the type of sensation ($F_{3,57} = 2.88,\ P < 0.001$) and bout of exercise ($F_{5,95} = 7.74,\ P < 0.001$), but not on the intake of placebo or tolperisone (Fig. 2A). Post hoc analysis showed that soreness VAS intensity was less than the warmth, tiredness and pain VAS intensity (SNK, $P < 0.03$) and that all these sensations were felt less in bout 1 as compared to bouts 2–6 (SNK, $P < 0.002$). In the placebo group, the average sensation of pain during six bouts of exercise correlated with the percent reduction in pressure pain thresholds at immediately after and 24 h (Spearman's $R = 0.51,\ P < 0.03$) and tiredness correlated only with the reduction in pressure pain thresholds at 48 h (Spearman's $R = -0.57$, $P < 0.001$). There were no correlations between sensations and pressure pain thresholds in the tolperisone group.

Equal number of subjects (two each) in the placebo and tolperisone group reported feeling of tightness/tenseness/swollen muscle during the intense eccentric exercise. Two subjects in the tolperisone group and one subject in the placebo group reported feeling of numbness during the intense eccentric exercise. Two subjects reported cramps in the placebo group, and one in the tolperisone group. All the subjects reporting immediate pain described it as deep, burning, or pulsating in nature. The mean tiredness VAS felt during intense eccentric exercise was (2.03 ± 0.66 cm) and there was no significant difference between the placebo and tolperisone group or between different bouts.

3.2. Self-assessment of pain by the patients on a Likert's scale (0–5)

Two-way RMANOVA showed no difference in effect of placebo or tolperisone on pain response of subjects on Likert's scale (0–5) (Fig. 2B). The pain increased as a function of time ($F_{4,76} = 28.38,\ P < 0.0001$) (Fig. 3). Post hoc analysis showed that pain increased at immediately after the bout 6, 24 h (day 7) and 48 h (day 8) after eccentric exercise as compared with before exercise (SNK, $P < 0.05$).

3.3. Pain areas

Two-way RMANOVA showed no difference in effect of placebo or tolperisone on pain areas (Arbitrary Units) drawn by the subjects (Fig. 2C). The pain areas increased as a function of time ($F_{4,76} = 12,\ P < 0.001$). Post hoc analysis showed that pain areas increased at immediately after the bout 6, 24 h (day 7) and 48 h (day 8) after eccentric exercise as compared with before exercise (SNK, $P < 0.05$).

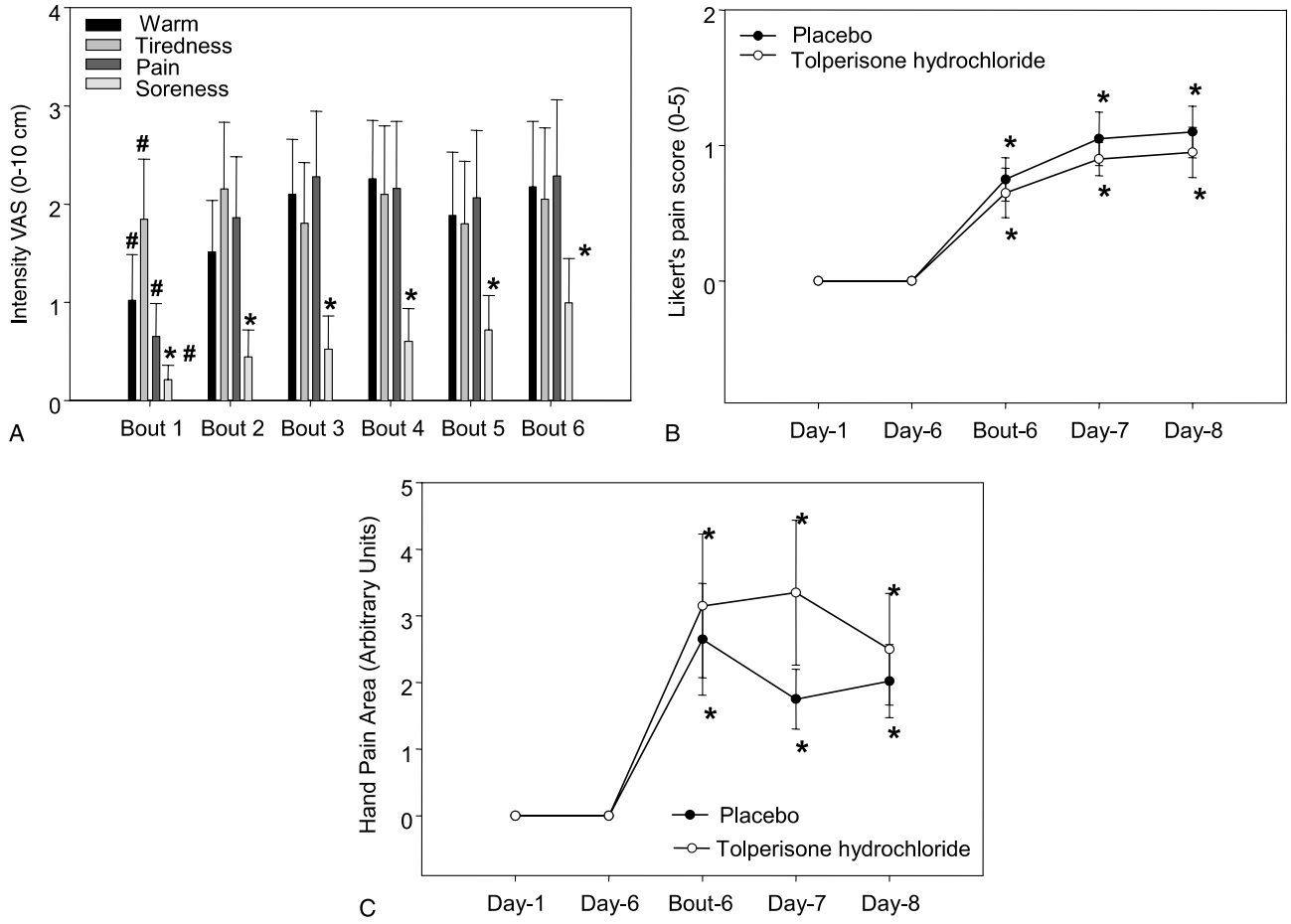

Fig. 2. (A) Bar chart showing the intensity VAS of sensations felt during different bouts of eccentric exercise. Soreness was less in all the bouts as compared to the feelings of warmth, tenderness and pain in the respective bouts ($^{*}P < 0.03$). # indicates that sensations were less in bout −1 as compared the bouts 2–6 ($^{\#}P < 0.002$). (B) Time course changes of Likert's pain score reported by the subjects. Higher pain was reported immediately after the exercise, and at days 7 (24 h) and 8 (48 h) as compared to days 1 and 6 ($^{*}P < 0.05$. (C) Time course changes of pain areas drawn by the subjects. Larger pain areas were drawn at immediately after the exercise, at days 7 (24 h) and 8 (48 h) as compared to days 1 and 6 ($^{*}P < 0.05$).

3.4. Pressure pain thresholds

Two-way RMANOVA analysis of time course changes in the percentage reduction in the exercised hand showed that PPT percentage reduction increased as a function of time ($F_{4,76} = 4.5,\ P < 0.03$) and that there was no difference between placebo and tolperisone (Figs. 3A and B). Post hoc analysis showed that PPT percentage reduction increased at 24 h (day 7) and 48 h (day 8) as compared with first baseline (day 1) (SNK: $P < 0.05$). The non-exercised hand showed no changes with time.

3.5. Range of motion

Three-way RMANOVA showed that the percentage reduction in range of motion did not change as a function of placebo or tolperisone. The percentage reduction in range of motion, however, was increased as a function of time ($F_{4,72} = 16.79,\ P < 0.001$), and hand ($F_{1,18} = 12.69,\ P < 0.03$) (Figs. 3C and D). There was also an interaction between time and hand ($F_{4,72} = 16.79,\ P < 0.001$). Post hoc analysis showed greater reduction in the range of motion in the exercised hand as compared to the non-exercised hand (SNK, $P < 0.03$), and immediately after bout 6 as compared to days 1, 6–8 (SNK, $P < 0.00$). The range of motion in the exercised hand was reduced (showed in Fig. 3 as an increase in percentage reduction) as compared to the non-exercised hand on the days 1, 6, immediately after day 7 (SNK, $P < 0.05$).

3.6. Isometric force

Three-way RMANOVA analysis showed that isometric force was reduced as a function of treatment (placebo/tolperisone) ($F_{1,19} = 8.45,\ P < 0.01$), time ($F_{4,76} = 9.32,\ P < 0.001$), and hand (exercise/non-exercise) ($F_{1,19} = 13.82, P < 0.001$) (Figs. 4A and B). There was an interaction between time and hand ($F_{4,76} =$

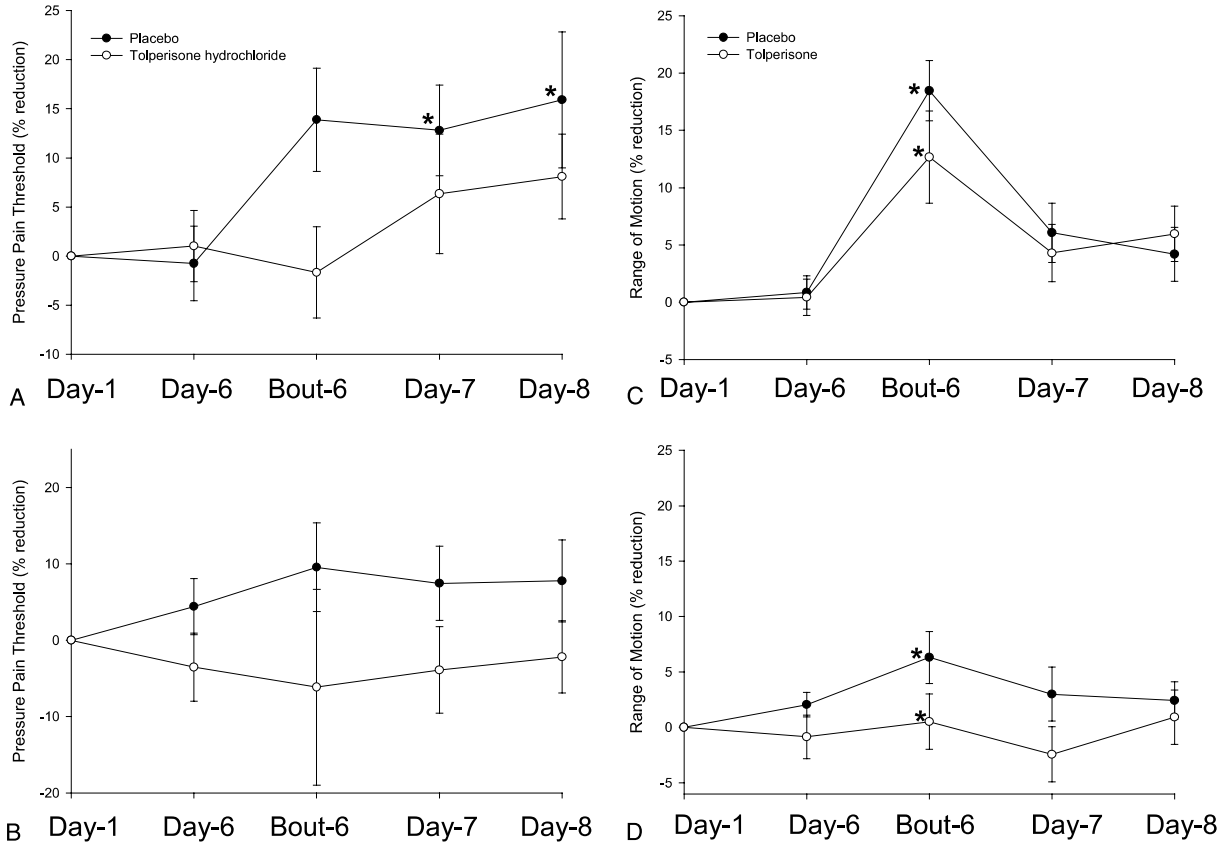

Fig. 3. The time course change of the percent reduction of (A) pressure pain threshold (PPT) of the first dorsal interosseous muscle in exercised (* indicates $P < 0.04$ on days 7 and 8 as compared to day 1 and day 6), (B) PPT in non-exercised hands, (C) range of motion (ROM) of the first dorsal interosseous muscle in exercised hand, (D) ROM in non-exercised hand (* indicates $P < 0.05$ at immediately after eccentric exercise as compared to days 1, 6–8).

10.11, $P < 0.001$). Post hoc analysis showed an overall reduction in the isometric force with tolperisone treatment as compared to placebo treatment (SNK, $P < 0.01$), in the exercised hand as compared to the non-exercised hand (SNK, $P < 0.02$); and immediately after exercise as compared to days 1, 6–8 (SNK, 0.03). The isometric force in exercised hand and non-exercised hand behaved differently at different times, overall in the exercised hand the force was lowest at immediately after (SNK, $P < 0.0002$) as compared to days 1, 6–8; and in the non-exercised hand, overall the force increased at immediately after, days 6–8 and as compared to that in the exercise (SNK, $P < 0.02$).

3.7. EMG RMS amplitude

Three-way RMANOVA analysis showed that EMG RMS amplitude recorded during maximum isometric force changed as a function of time ($F_{4,76} = 6.79$, $P < 0.0001$) (Figs. 4C and D). There was an interaction between time and hand ($F_{4,76} = 2.78$, $P < 0.04$), i.e., the exercised hand and non-exercised hand behaved differently at different times, but overall there was no significant difference between the two hands. Post hoc analysis showed that reduction in EMG RMS occurred immediately after the exercise (SNK, $P < 0.04$) and EMG RMS amplitude increased in the exercised as compared to the non-exercised hands on day 7 and 8 (SNK, $P < 0.003$). There was no difference between the placebo and the tolperisone treatment groups. One-way RMANOVA showed that EMG RMS was reduced immediately after the exercise in the exercised hand of the placebo group (SNK, $P < 0.05$) and gain in EMG RMS amplitude occurred in the tolperisone group in the exercised hand (SNK, $P < 0.05$).

3.8. Adverse events

No serious adverse events were documented in the course of the study. None of the subjects on placebo complained of any side effects. The adverse events reported were tight stomach, water brash, headache, weakness and tremor. All adverse events were of mild or moderate intensity and were cured without damage. Total six adverse events in 4 volunteers occurred in the tolperisone group. For 5 of these adverse events the relationship to the study medication was assessed "at least possible" by the responsible drug safety manager

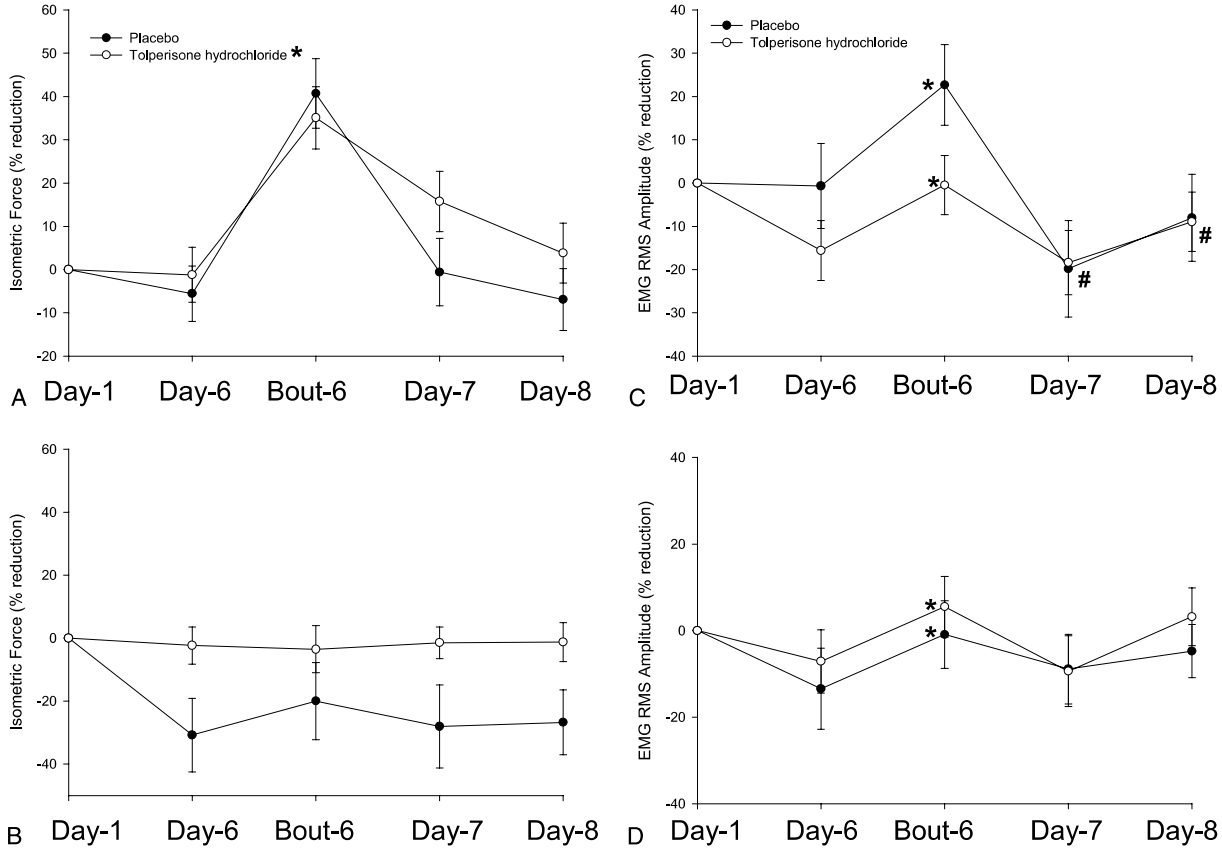

Fig. 4. The time course change of the percent reduction of (A) isometric force of first dorsal interosseous muscle in exercised hand. (B) Isometric force in non-exercised hand (* indicates $P < 0.01$ in tolperisone as compared to placebo; (C) EMG RMS (mV) recorded during the isometric force assessments of first dorsal interosseous muscle in exercised hand (# indicates $P < 0.003$ as compared to the non-exercised hand); (D) EMG RMS in non-exercised hand (* indicates $P < 0.04$ at the end of bout 6 as compared to days 1, 6–8).

(PB, the first author). The relationship to the study medication of the sixth adverse event (“excessive sweating of the feet”) was assessed as “unlikely”.

4. Discussion

The main finding in the present paper was that an oral dose of 150 mg tolperisone taken thrice daily for six days prior to eccentric exercise resulted in reduced isometric force but had no prophylactic effect on the development of pain and soreness after a strenuous exercise and in the post-exercise muscle soreness. Assessment of pain on Likert’s pain scale and pain drawings made by the subjects and reduced PPT indicated the presence of PEMS at 24 and 48 h after eccentric exercise in both placebo and tolperisone groups.

4.1. Isometric force

The time course changes showed that the isometric muscle force generation greatly reduced at immediately after the eccentric exercise and the reduction persisted till 48 h. The time course changes in isometric force was different than the time course changes of PEMS. Reduction of isometric strength of elbow flexor muscles did not recover till five days of eccentric exercise (Ebbeling and Clarkson, 1989). This reduction of force indicates fatigue and was also indicated as increased subjective sensations of tiredness. Fatigue has been defined physiologically as a reduced capacity to sustain force or power output (Kaasa et al., 1999). The relationship between skeletal muscle damage, muscle soreness and loss of muscle force is unclear. Training results in attenuation of pain but reduction in muscular strength still persists till 2–3 days, suggesting that the two may have different physiological origins (Pierrynowski et al., 1987). In the present study the eccentric exercise resulted in reduced isometric force generation, and more so in the individuals under the influence of tolperisone. Eccentric exercise muscle damage is associated with an altered proprioception and feeling that individuals are producing more force, when they actually are producing less force as has been demonstrated earlier (Miles et al., 1997; Saxton et al., 1995). Tolperisone appears to disturb the central commands which determine the sense of force or may enhance the damage to Golgi tendon organs which are the primary determinant of the tension

information to the central nervous system (Basmajian and Deluca, 1985; Jones, 1990).

The force reduction occurred till 48 h after the exercise only in the tolperisone group, while in placebo group the isometric force returned to baseline at 24 h. This suggests that the muscle relaxation achieved by the prophylactic administration of tolperisone may result in enhancement and prolongation of force reduction after eccentric exercise. Tolperisone has been shown to be an effective muscle relaxant in a highly resistant case of tardive dystonia (Nisijima et al., 1998). It has been suggested that tolperisone's depression of flexor reflex mediated by group II afferent fibres is partly mediated by inhibition of noradrenergic tonic facilitation within the spinal cord (Sakitama, 1993). In another study tolperisone reduced masseter muscle excitability in healthy males (Takata et al., 1996). Tolperisone has been used in previous experiments with rodents for the purpose of inducing motor impairments (Doi and Sawa, 1980) and in a recent study tolperisone has been shown to produce a characteristic motor deficit in mice (Ikeda et al., 2001). Tolperisone hydrochloride also produces transient and long-lasting depression of mono and polysynaptic reflex potential in anaesthetized mice (Okada et al., 2001).

In the present study one of the subjects stopped tolperisone treatment due to feeling of weakness and one subject felt excessive sweating during last 5 days of treatment. None of the subjects required any treatment for these side effects. Earlier, a battery of psychomotoric tests and mood ratings showed that tolperisone in repeated doses of 50 and 150 mg has no sedative effects (Dulin et al., 1998). The sedative effects were present in 0.8% in Dulin et al. (1998) study, which was far below the incidence reported on placebo in controlled trials with other muscle-relaxing drugs (Dapas et al., 1985; Smith et al., 1994; Wallace, 1994). In rat experiments, tolperisone did not potentiate the effects of alcohol with respect to alcohol induced sleep or craving for alcohol (Dulin et al., 1998). On the basis of these results it can be suggested that tolperisone hydrochloride is an effective muscle relaxant that does not cause any sedation.

4.2. Sensations and pain during and immediately after eccentric exercise

After the first bout of exercise consistently increased sensations of warmth and tiredness were reported till the sixth bout of exercise. Pain, however, gradually increased with an increase in the number of exercise bouts. A subjective experience of feeling exhausted, tired, weak, or having lack of energy is defined as a fatigue (Wessely, 1995) and therefore it indicates that in the present study the eccentric exercise protocol effectively resulted in muscle fatigue. It is suggested that the characteristics of pain during or immediately after isometric or concentric exercise are attributed to an occlusion of blood flow on the basis that the pain subsides quickly as the contractile activity is terminated and blood flow is restored (Cook et al., 1997; Miles and Clarkson, 1994). In the present study we demonstrated that the prophylactic treatment with placebo or tolperisone for 6 days prior to intense eccentric exercise of FDI in healthy individuals had no effect on the sensations felt immediately after the eccentric exercise (warmth, tiredness, pain and soreness). What exactly causes these feelings of warmth, tiredness, pain and soreness during eccentric exercise is unclear and is an area that needs further investigations. The ratings of perceived exertion do not fully correlate with the blood lactate levels, suggesting that the cause must be in other aspects of muscular contraction (Ljunggren et al., 1987). For example, it could be that neuromuscular signal transmission is hampered, proprioception is disturbed, or there is a dysfunction of the contractile elements (Bajaj et al., 2001d; Friden et al., 1983). In the present study sensation of tiredness and pain during the exercise in the placebo group correlated with the pressure pain thresholds after the exercise and this suggests that these sensations during the exercise act like protective and warning mechanisms for reducing the post-exercise muscle soreness.

4.3. Post-exercise muscle soreness

The time course changes of the Likert's pain score, pain area and pressure pain threshold in the present study showed that post-exercise muscle soreness persisted till 24 and 48 h. The peak reduction in PPT occurred at 24 and 48 h. This is in accordance with the earlier studies on experimental post-exercise muscle soreness induction in the FDI muscle of hand (Bajaj et al., 2000, 2001d). The lack of effects of tolperisone on PPT, Likert's pain scores and pain areas suggests that tolperisone when used alone, has no effect on relieving PEMS. In another study, morphine but not tolperisone effectively increased the pain thresholds in the post-stress session (Doi and Sawa, 1980). Tolperisone although a muscle relaxant, also has a lidocaine-like activity (Fels, 1996). It acts by blocking sodium channels and thus stabilizes nerve membranes (Ono et al., 1984), however recently it has been suggested that tolperisone cannot be said to have a so-called lidocaine-like activity, because there were effects shown on potassium permeability (Hinck and Koppenhofer, 2001). In a randomized controlled clinical trial beneficial effects of tolperisone in painful reflex muscle spasm in patients with disorders of the spinal column or proximal joints could be demonstrated. There was a significantly higher increase in PPT that was the result of compilation of means of 16 symmetrical standard myofascial pressure points and the point of maximum pain in comparison to the placebo treatment (Pratzel et al., 1996). Another

recently performed randomized controlled trial investigating the effects of tolperisone on experimentally induced jaw-muscle pain in healthy volunteers showed, that tolperisone provides a small, but significant reduction in the perceived intensity of experimental jaw-muscle pain whereas the present dose had no effect on the short-latency jaw-stretch reflex (Svensson et al., 2002). The results in the present study suggests that further investigations are required before the lidocaine-like effect of tolperisone on PPT can be finally confirmed.

4.4. Range of motion

Muscle damage can be assessed and quantified indirectly by functional parameters, such as range of motion or ability to exert force. In the present study reduced range of motion was seen immediately after the exercise that lasted till 48 h. As compared to non-exercised hand, the range of motion was still reduced at 24 h. Placebo or tolperisone treatment did not alter the time course changes in range of motion. Reduced range of motion suggests the association of stiffness, reduced joint flexibility and joint function with PEMS (Ellis et al., 1997). ROM in eccentric exercise of elbow flexors was attributed to the presence of oedema (Jones et al., 1987). Exercise induced damage to the muscle/tendon complex and the presence of prolonged impairment of motor skills may be due to the loss in force generating capacity, change in proprioceptive feedback, or alteration in corticomotor control (Pearce et al., 1998). Again the reduction in ROM can be seen as a protective response towards painful stimuli (Lund et al., 1991).

4.5. EMG RMS amplitude

Reduction of the EMG RMS amplitude immediately after the eccentric exercise in the present study as a result from the concomitant reduced ROM and reduced isometric force was in accordance with earlier studies (Clamann, 1970). More recently it was shown that EMG RMS decreased after intense eccentric and concentric exercises (Linnamo et al., 2000). In contrast to placebo, the subjects on tolperisone in the present study showed no reduction or slight increase in EMG RMS amplitude immediately after the exercise, suggesting that the FDI was relaxed and required greater neural input to produce maximum voluntary isometric force. De Vries criticized Hough's torn-tissue hypothesis in 1960s, when he demonstrated that PEMS was associated with increased EMG RMS, and both PEMS and EMG RMS revert back to normal after the application of the stretching treatment (de Vries, 1966). It was then suggested that PEMS is caused by tonic localized spasm of motor units, whose numbers vary with the severity of pain, and it was proposed that substance-P and ischemia cause more substance-P release resulting in a vicious cycle of spasm–pain–spasm (de Vries, 1966). It is suggested that a non-contracting muscle shows no EMG activity, and the contracting muscle has electrical activity roughly proportional to the tension in its muscle fibres (Boivin et al., 1969) and it has been shown to be true for isometric contractions (Close et al., 1960) and this was the reason that we chose to record EMG during isometric contractions only in the present study.

In a rat rigidity model, tolperisone was shown to have a long-lasting reduction in EMG potentials and muscle tone of triceps surae suggestive of its potent muscle relaxant activity (Matsunaga et al., 1997). Pain has been shown to produce protective muscle spasm and a reduction in the joint angle (Sessle et al., 1999), however other EMG studies have provided no evidence for this phenomenon (Howell et al., 1985; Jones et al., 1987). EMG studies have demonstrated an evidence of inhibition of the motor unit activity and an alteration in the activation strategy at a whole muscle level as a result of PEMS (Bajaj et al., 2001c; Madeleine et al., 2000). Presently evidence is emerging that noxious stimulus to a muscle is likely to cause relaxation of the stimulated muscle by inhibition of homonymous α-motor neurons (Lund et al., 1991; Mense et al., 2000), moreover, the painful muscle frequently show no resting electrical activity (Johnson, 1989; Norris et al., 1957; Walsh, 1992).

4.6. Conclusion

On the basis of the present study we conclude that the prophylactic administration of tolperisone (150 mg thrice daily) results in reduced isometric force without having a pain relieving effect on PEMS. Indirectly we can speculate that muscle spasm does not contribute to the causation of PEMS. Finally, the findings do not support the medication for athletes before competition or workers who needs muscle power in their work.

Acknowledgements

This study was supported by a grant from the Danish National Research Foundation. We would also like to thank Katrin Kuhn, MD for commenting on the manuscript and Strathmann AG, Germany for generous supply of tolperisone hydrochloride and placebo tablets.

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