

Comparison of the Effects of Joint Mobilization, Gym Ball Exercises, and Breathing Exercises on Flexion Relaxation Phenomenon and Pain in Patients with Chronic Low Back Pain

Background: Although various exercises have been performed for patients with chronic low back pain (CLBP), the effects of these exercises including joint mobilization, gym ball exercises, and breathing exercises on flexion relaxation ratio (FRR) have not been compared.

Objective: To compare the effects of joint mobilization, gym ball exercises, and breathing exercises on the flexion relaxation phenomenon (FRP) and pain in patients with chronic low back pain.

Design: Randomized pretest–posttest control group design.

Methods: Thirty–six patients with chronic low back pain who were undergoing rehabilitation at a rehabilitation center were included. The patients were randomly divided into three groups: joint mobilization group (JMG; n=12), gym ball exercise group (GBG; n=12), and breathing exercise group (BEG; n=12). The exercises were performed for 40 minutes a day, twice a week, for a total of 12 weeks.

Results: There were no significant differences in FRR between the three groups ($P>.05$). Significant decreases in the modified visual analog scale (MVAS) scores after intervention between the groups were found ($P<.05$). The GBG was significantly decreases from the JMG in the MVAS ($P<.05$). However, there were significant improvements between the pre– and post–interventional findings on FRR and MVAS in the three groups ($P<.05$).

Conclusion: We demonstrated that intervention using joint mobilization, gym ball exercises, and breathing exercises improve FRP and pain in patients with CLBP.

Keywords: Breathing exercise; Flexion relaxation phenomenon; Joint mobilization; Gym ball; Chronic low back pain

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INTRODUCTION

Back pain is a current problem that has been discussed extensively in the literature worldwide, but its exact etiology is still debated.^{1,2} Previous studies have identified multiple risk factors for back pain, including genetic factors, obesity, habits such as smoking, psychological factors, and biomechanical factors, in which the magnitude of the mechanical load on the spine is highly related to back pain.³⁻⁷

An excessive mechanical load on the lumbar spine can lead to intervertebral disc rupture or spinal fracture, and a strong association between spinal load (compression, shear force) and the prevalence of lumbar pain has been found.⁸ Thus, a comprehensive understanding of spinal biomechanics is important for appropriate control strategies that reduce the risk of back pain while performing weight-bearing tasks.

A flexion relaxation phenomenon that occurs when the spine is in full flexion: the spinal extensors relax

completely and the flexion torque is supported by the spinal ligaments. Therefore, during weight-training, it is especially important to use the correct technique when the spine is fully flexed because the tension in the spinal ligaments adds significantly to the anterior shear force on the lumbar vertebrae and increases the load on the facet joints.⁹ The flexion relaxation phenomenon (FRP) refers to the erector spinae (ES) muscles losing EMG activity (myoelectric silence) at the end of trunk flexion.¹⁰ In healthy subjects, the myoelectric silence during trunk flexion is thought to be caused by the stretch inhibition reflex. The temporal and spatial recruitment changes of the spinal muscles in patients with chronic low back pain during daily activities or walking and paraspinal muscle activity during mobility of the trunk and limbs is significantly higher than that in normal muscles and can also lead to abnormal movement control.¹¹⁻¹⁴ Currently, two theories of FRP have indicated that moment changes of passive tissues, such as ligaments or the lumbodorsal fascia, and the redistribution of muscle recruitment in deep muscles are difficult to measure by electromyography.^{15,16} Also The flexion relaxation ratio (FRR), a comparison of the maximal sEMG activity during 1 s of forward flexion with activity in full flexion, demonstrated significantly lower values in the CLBP than the control group. The combined discriminant validity for the FRR for all four sites resulted in 93% sensitivity and 75% specificity.⁸

Patients with chronic low back pain have neuromechanical receptors in the joint tissues, articular capsules, and ligaments that are stimulated by active and passive movement of the joints.¹⁷ When these joint tissues are deformed within the limits of normal tissue elongation, nociceptors are activated, causing pain responses. Pain is transmitted by nociceptors, also known as specialized peripheral sensory neurons.¹⁸ Nociceptors convert these stimuli into electrical signals that are delivered to higher brain centers, indicating that they are damaging stimuli that can potentially damage the skin.¹⁸ If noxious stimulus persists, peripheral and central sensitization will occur leading to the transition of acute pain to chronic pain.¹⁹

Many approaches have been used to improve FRP and pain in patients with chronic low back pain, Lumbar joint mobilization, lumbar pelvic stabilization exercise, diaphragmatic strengthening exercises, and respiratory exercises that raise awareness of cognitive ability and respiratory movement through processes such as auditory and tactile feedback and motor control are being studied as treatment methods for

chronic back pain associated with respiratory failure.²⁰⁻²⁴ In particular, gym ball exercises have been widely used in clinical practice for many years. These improve pelvic and spinal stability and help intrinsic sensation and posture control by activating the local muscles in patients with chronic low back pain.²⁵

In addition, Sremakaew et al²⁶ found that cervical spinal mobilization, stabilization, and proprioceptive training improved afferent sensory input and pain in previous intervention studies, although these results have not been fully explained. Another research reported that diaphragmatic breathing exercise improves activation of trunk muscle of patients with low back pain.²⁷ Therefore, it is more being discussed whether various interventions included the breathing exercises are appropriate interventions for change FRR and the treatment of chronic back pain.²⁸

Therefore, the purpose of this study was to understand the effects of joint mobilization, gym ball exercises, and breathing exercises on biomechanical changes and pain in patients with chronic low back pain and to compare the effects on inter-group variables.

SUBJECTS AND METHODS

Subjects

This study was a two-arm, parallel, randomized controlled trial with concealed allocation and researcher and assistant blinding. Patients in a rehabilitation center who had been experiencing chronic low back pain for at least 12 months were included in this study. The inclusion criteria were as follows: (1) nonspecific chronic low back pain and mechanical chronic low back pain and (2) an understanding of agreement with the contents of this study. The exclusion criteria were as follows: (1) orthopedic or neurological surgery, (2) cardiovascular disease or high risk of falls, (3) other chronic pain, (4) participation in other exercise programs (abdominal muscle training within 1 year), (5) pregnancy in the previous 2 years, (6) malignant tumor, or (7) radiating pain to two sites.²⁹ All patients understood the requirements of the study and provided informed consent before their participation. All procedures were approved by our Institutional Review Board.

Outcome Measure

Electromyography

In this study, to measure the surface electromyography

of the FRR, an electromyogram (EMG) (MyoTrace 400, Noraxon Inc Arizona, USA) was taken of the multifidus (MF) and ES during trunk flexion and extension (Figure 1A). To reduce the skin resistance of the surface EMG signal, the electrode attachment site was waxed, exfoliated with fine sandpaper, and then disinfected with an alcohol-soaked cotton swab. The surface electrodes were 0.5 cm in diameter and were placed at an interelectrode distance of 2 cm; these electrodes were made of Ag/AgCl and filled with conductive gel. The EMG sampling rate was fixed at 1,000 Hz, the frequency bandwidth was fixed between 20 and 500 Hz, and the filter process was performed. The surface EMG signal from each muscle during trunk flexion and extension was processed by the root mean square.

The FRR was measured by EMG on the patients MF and ES, and surface EMG records were obtained on both sides. For the MF, electrodes were placed at the level of L5, on the line between the posterior superior iliac spine (PSIS) and the point between L1 and L2; for the ES, electrodes were attached 3 cm lateral to the spinous process of L3 (Figure 1B).^{30,31}

Pain assessment (modified visual analog score)

Before and after the intervention, all patients' pain levels were assessed according to the modified visual analog scale (MVAS) scores. The patients were required to use a "V" to make a mark between "0" to "10" on a scale that consists of a 100 mm line; "0" means no pain and "10" means severe pain. The score

for each item was measured in centimeters from the zero point of the MVAS to the location marked by the subject, corrected to one decimal place.³²

Experimental Procedures

The following pre-test general characteristics of the patients were assessed: sex, age, weight, height, and subjective pain assessments. Baseline data of both MF and ES surface EMG were obtained before and after the study. The diaphragmatic breathing pattern was an up and down motion of the diaphragm, performed by a therapist, who demonstrated an accurate method of respiration. A subject in a hook lying position was asked to put his/her hands on the rectus abdominis muscle immediately below the anterior costal cartilage, and to inhale slowly and deeply only by swelling his/her abdomen without moving his/her upper chest while relaxing his/her shoulders. Then, the subject exhaled all the air slowly. During inhalation, the air was breathed in through his/her nose, and his/her abdomen was swollen. After the breath was suspended at the last moment, the subject exhaled the air according to the pursed lip breathing, with which the subject breathed out the air through his/her mouth with his/her lips half-opened and his/her abdomen made hollow. One breathing consisted of three seconds of inhalation, three seconds of suspension, and six seconds of exhalation. A subject was asked to put one hand on the chest and the other one on the abdomen, not to show movement of the

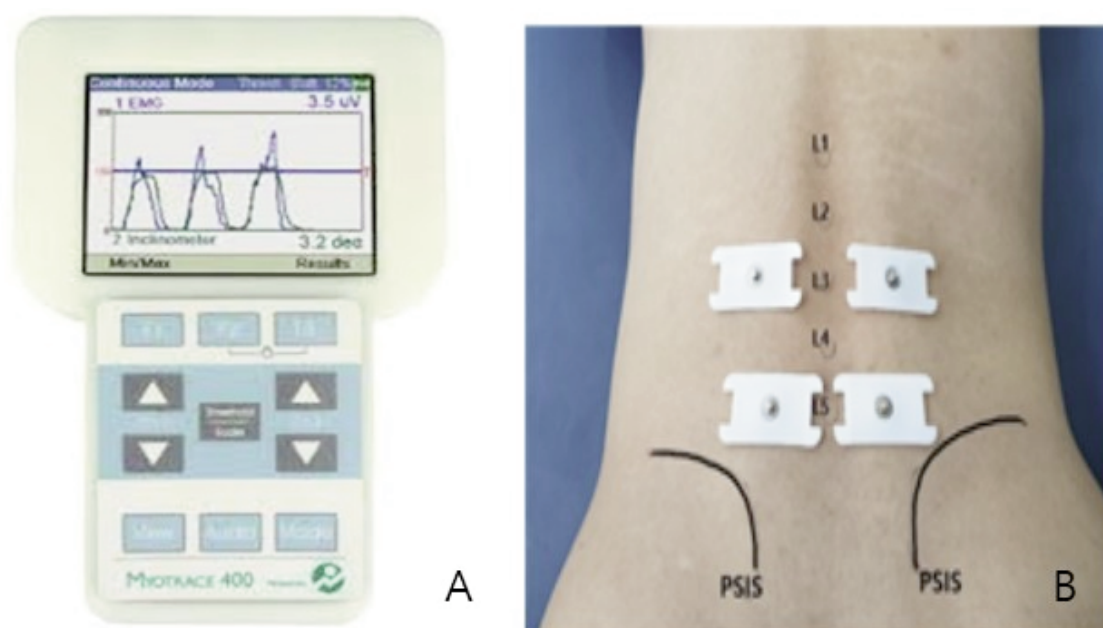


Figure 1. (A) MyoTrace 400 (Noraxon Inc Arizona, USA), (B) SEMG Sensor placement (Multifidus, erector spinae).

upper chest.³³ The protocol started with subjects standing with the electrodes attached and their feet hip distance apart. Patients stood up straight for 3 seconds (step 1) and then bent forward as much as possible (step 2). Patients were asked to tuck their chin to their chest while bending forward depending on the impact of the surface electromyography (SEMG) activity. In step 3, patients were requested to maintain maximum voluntary flexion (MVF) for 3 seconds and then return to an upright position for 3 seconds (step 4). Patients were asked to repeat these steps three times (Figure 2). In each of the four stages, the maximum muscle activity was measured for 1 second. To normalize the data, the data collected in steps 2, 3, and 4 were divided by the mean SEMG activity in step 1.³⁴ These data were used to calculate the flexion relaxation ratio (FRR).

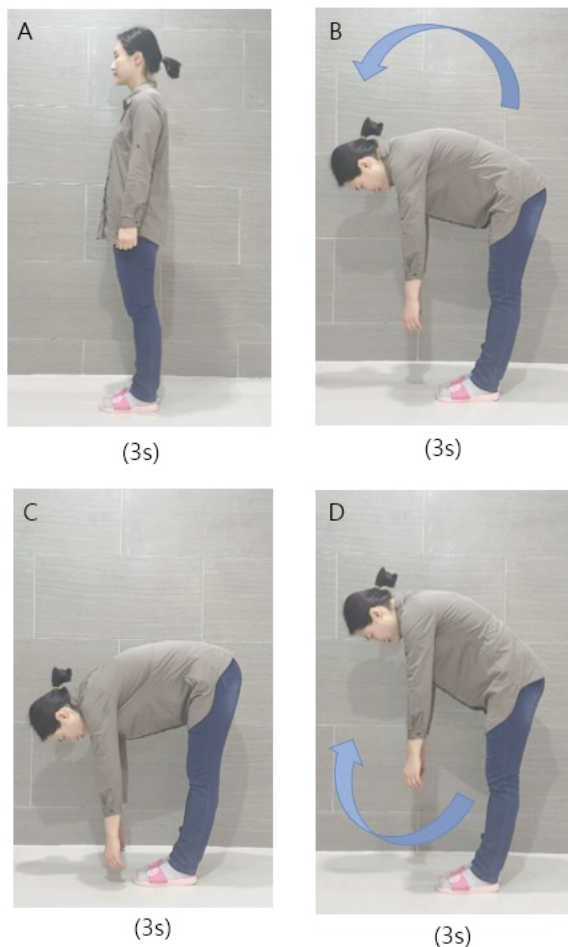


Figure 2. Functional task.

- (A) Quiet standing (step 1),
- (B) Flexion of the trunk lasting 3 seconds (step 2),
- (C) Maximum voluntary flexion lasting 3 seconds (step 3),
- (D) Extension of the trunk lasting 3 seconds (step 4).

- 1) FRR comparing normalized muscle activity during flexion (step 2) over MVF section: Flex/MVF
 - 2) FRR comparing normalized muscle activity during extension (step 4) over MVF section: Ext/MVF
- The damage of flexion relaxation is reflected in the low FRR value.³⁴

Intervention

Joint mobilization (JMG)

Joint mobilization was performed in three stages for recovery of pain and motion. In the first stage, the joint at the treatment site was left slack, and in the second stage, the joint slack was taken up before the joint is stretched. Stretching was performed in stage 3. Stages 1 and 2 were used to alleviate pain, and stage 3 was used to increase mobility. Initiation of treatment was followed by a rest position and then traction and slipping. When both muscles and joints were abnormal, general massage was first performed to the muscles, followed by functional massage to both the muscles and joints. Finally, mobilization was performed using three stages of traction and slipping.³⁵ The patients underwent joint mobilization for 40 minutes, twice a week, for 12 weeks by a physical therapist who had been certified through a Kaltenborn orthopedic physiotherapy spine course.

Gym ball exercises (GBG)

The first six weeks of exercises included side bridging, gym ball partial-curl ups, supine bridging with single leg raise, prone bridge, and quadruped exercise on a relatively stable support, while the next six weeks included push-ups, gym ball single leg holds, and gym ball roll-outs performed on an unstable support. The gym ball exercises were applied to improve lumbar spine stability and to increase muscle activity in the abdomen.³⁴ The patients underwent gym ball exercises for 40 minutes, twice a week, for 12 weeks by a physical therapist.

Breathing exercises (BEG)

The respiratory exercises were designed to maintain the neutral alignment of the spine by retraining the breathing pattern through relaxed diaphragm breathing as the first method by applying the Doming technique, which relieves the diaphragm rest state and improves diaphragm contraction and relaxation function.³⁶ The patient sat at the treatment table in a comfortable and relaxed position, and from behind, the therapist wrapped his or her hands under the rib cage and pressed with the fingers. The therapist carefully turned to the left and right sides where the

rib cage moves freely and comfortably to determine the appropriate direction and attempted to relax the diaphragm in the direction with ease of movement. This posture was held for 5 minutes (Figure 3). The second method involved training and correcting breathing patterns by 1) recognizing abnormal breathing patterns, 2) relaxing the jaws, upper chest, shoulders, and accessory respiratory muscles, 3) retraining abdominal/diaphragm breathing patterns, normal breathing frequency, rhythm, and talking at rest, and 4) training awareness of the respiratory rate and rhythm during activity.³⁷ Third, the patient was educated on normal breathing patterns for functional movements corresponding to daily life with various postures and movements.³⁸ The patients underwent



Figure 3. Doming technique for the diaphragm.

breathing exercises for 40 minutes, twice a week, for 12 weeks by a physical therapist.³⁹

Data analysis

The Kolmogorov–Smirnov test was used to determine the normal distribution of all data through technical statistical analysis and analysis of variance (ANOVA); the general characteristics of respondents and homogeneity between groups were recorded. Multivariate ANOVA was used to analyze the differences between dependent variables (FRR and pain) according to the measurement period (before and after the experiment) and the intervention method; statistically significant differences were evaluated by Tukey's HSD. The significance level was set at $\alpha=.05$. All data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 90 patients were admitted to the rehabilitation center, and 42 fulfilled the inclusion criteria. Participants were randomly assigned to the joint mobilization group (JMG; $n=14$), the gym ball exercise group (GBG; $n=13$), or the breathing exercise group (BEG; $n=15$). Thirty-six participants completed the study (Figure 4). General baseline characteristics are shown in Table 1.

Table 1. The general characteristics of the subjects.

	JMG (n=12)	GBG (n=12)	BEG (n=12)	F	P
Sex (Male/Female)	4/8	6/6	4/8	.440	.648
Age (years)	45.33 \pm 10.27	41.00 \pm 6.38	43.33 \pm 10.26	.673	.517
Height (cm)	165.56 \pm 6.28	166.20 \pm 8.72	165.44 \pm 6.95	.036	.964
Weight (kg)	63.00 \pm 7.16	65.80 \pm 7.84	63.25 \pm 7.01	.535	.591
BMI (score)	22.90 \pm 1.24	23.76 \pm 1.46	23.01 \pm 1.80	1.139	.332
MVAS (score)	4.91 \pm 1.08	5.66 \pm 1.30	5.00 \pm 1.04	.625	.538

values are presented as mean \pm SD or number only

BMI: Body mass index, MVAS: Modified visual analog score

JMG: Joint mobilization group, GBG: Gym ball group, BEG: Breathing exercise group

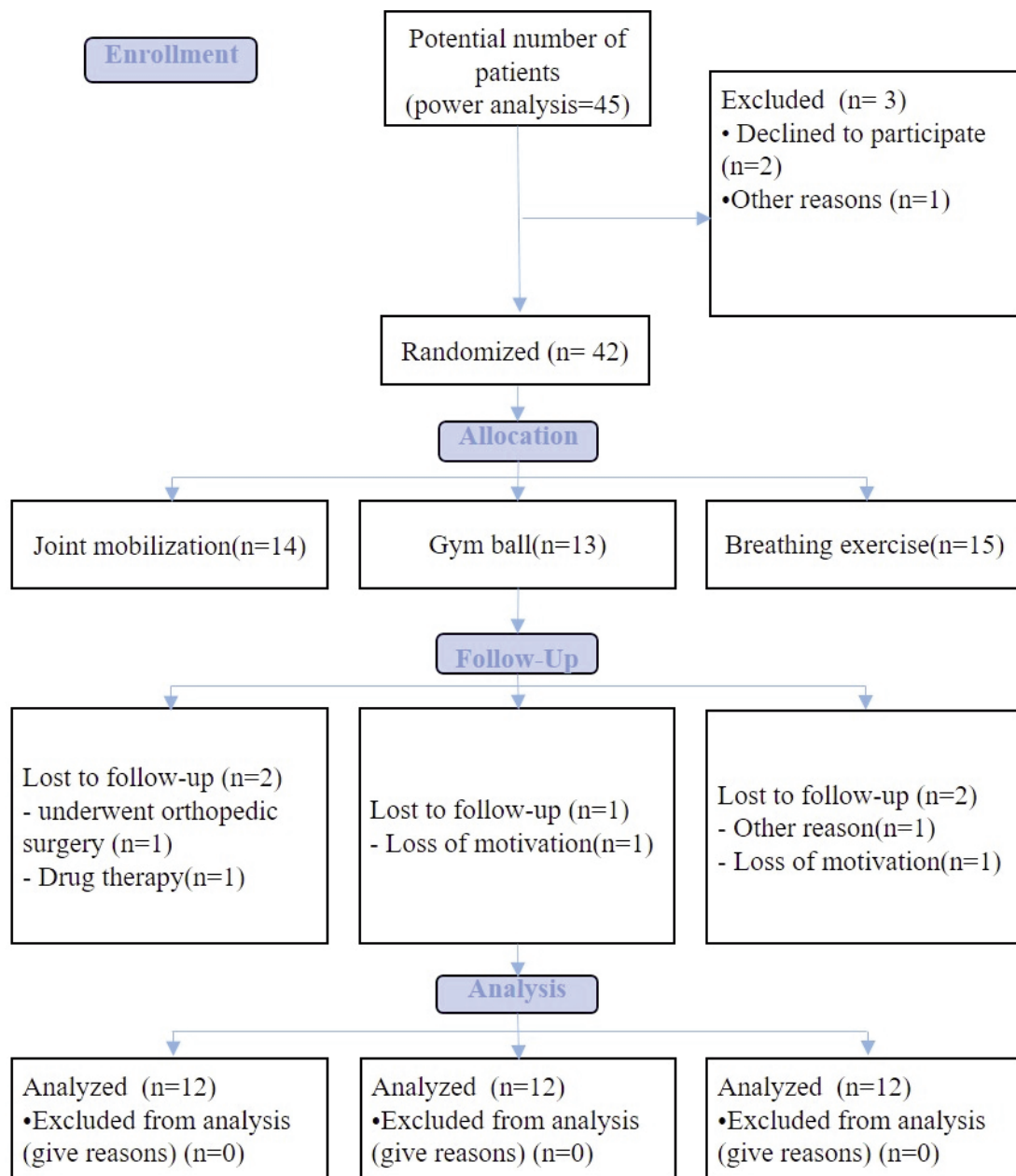


Figure 4. Flow diagram of this study. Forty-five individuals were enrolled in the study and were randomly assigned to the joint mobilization group (n=14), the gym ball group (n=13) or the breathing exercise group (n=15).

Comparison of the ES and MF in FRR

A comparison of the ES and MF in FRR before and after intervention among the three groups is presented in Table 2. Significant increases in ES FRR (Flex/MVF), ES FRR (Ext/MVF), MF FRR (Flex

/MVF), and MF FRR (Ext/MVF) before and after intervention were found in the JMG, GBG and BEG ($P < .05$) except MF FRR (Ext/MVF) in BEG ($P > .05$). There was no statistically significant difference in the FRR in the ES and MF between the three groups ($P > .05$) (Table 3).

Table 2. Descriptive data for flexion relaxation ratio of the erector spinae and multifidus by exercise group. (n=36)

Variable	Pre	Post	t (P)
ES FRR (Flex/MVF)			
JMG	1.16 ± .33	5.06 ± .369	-3.50 (.005)**
GBG	1.35 ± .92	5.85 ± 4.00	-3.97 (.002)**
BEG	1.05 ± .20	5.06 ± 4.52	-3.03 (.011)*
ES FRR (Ext/MVF)			
JMG	1.45 ± 1.01	11.94 ± 8.07	-4.30 (.001)**
GBG	1.82 ± 2.21	14.45 ± 10.37	-4.09 (.002)**
BEG	1.31 ± .56	11.41 ± 10.48	-3.32 (.007)**
MF FRR (Flex/MVF)			
JMG	1.32 ± .85	4.23 ± .3.32	-2.77 (.018)*
GBG	1.24 ± .67	4.36 ± 3.57	-2.83 (.016)*
BEG	1.73 ± 2.24	5.65 ± 5.24	-2.32 (.040)*
MF FRR (Ext/MVF)			
JMG	1.74 ± 1.82	9.35 ± 9.20	-2.69 (.021)*
GBG	1.64 ± 1.35	10.53 ± 10.41	-2.83 (.016)*
BEG	2.58 ± 4.43	10.99 ± 11.96	-2.17 (.053)

**P < .01, *P < .05, values are presented as mean ± SD

ES: Erector spinae, MF: Multifidus, FRR: Flexion relaxation ratio, MVF: Maximum voluntary flexion

JMG: Joint mobilization group, GBG: Gym ball group, BEG: Breathing exercise group

Table 3. Comparison of changes in flexion relaxation ratio among groups. (n=36)

Variable	JMG (n=12)	GBG (n=12)	BEG (n=12)	F (P)
ES FRR (Flex/MVF)	-3.90 ± 3.85	-4.50 ± 3.92	-4.14 ± 4.02	.71 (.931)
ES FRR (Ext/MVF)	-10.49 ± 8.44	-12.62 ± 10.68	-10.09 ± 10.50	.22 (.799)
MF FRR (Flex/MVF)	-2.91 ± 3.63	-3.11 ± 3.80	-3.92 ± 5.85	.16 (.847)
MF FRR (Ext/MVF)	-7.61 ± 9.78	-8.89 ± 10.88	-8.41 ± 13.41	.03 (.962)

values are presented as mean ± SD

ES: Erector spinae, MF: Multifidus, FRR: Flexion relaxation ratio, MVF: Maximum voluntary flexion

JMG: Joint mobilization group, GBG: Gym ball group, BEG: Breathing exercise group

Table 4. Descriptive data for pain by exercise groups. (n=36)

Variable	Pre	Post	t (P)
MVAS (score)			
JMG	4.92 ± 1.08	3.33 ± .98	6.09 (<.001)**
GBG	5.66 ± 1.30	2.66 ± 1.15	6.51 (<.001)**
BEG	5.00 ± 1.04	2.67 ± 1.15	7.00 (<.001)**

**P < .01, Values are presented as mean ± SD, MVAS: Modified visual analog score

JMG: Joint mobilization group, GBG: Gym ball group, BEG: Breathing exercise group

Table 5. Comparison of intergroup intervention on pain.

(n=36)

Variable	JMG (n=12)	GBG (n=12)	BEG (n=12)	F (P)
MVAS (score)	1,58.90 ± 0.90	3,00 ± 1.59*	2,33 ± 1,15	3,85 (.031)*

* $P < .05$ (Significant difference in a comparison with the JMG), Values are presented as mean ± SD
 JMG: Joint mobilization group, GBG: Gym ball group, BEG: Breathing exercise group

Comparison of the pain

A comparison of the MVAS scores before and after intervention among the three groups is presented in Table 4 ($P < .01$). Significant decreases in the MVAS scores after intervention were found between the groups ($P < .05$). Post-hoc tests revealed that the GBG was significantly decrease from the JMG in the MVAS scores ($P < .05$) (Table 5).

DISCUSSION

This study was conducted to compare the effects of joint mobilization, gym ball exercises, and breathing exercises on FRP and pain in patients with chronic low back pain. The FRP of the lumbar spine is the myoelectric silence of the EMG activity at the end of trunk flexion,¹⁰ and in healthy subjects, electrical silence during trunk flexion is thought to be caused by the stretch inhibition reflex. In patients with chronic back pain, the increase in activity during full trunk flexion may be due to changes in lumbar afferent sensations. Previous studies have shown that the mechanical receptors and nociceptors connected to spinal ligaments and disks react to the load, movement, and inflammation in the joints.^{40,41} In this study, there was no statistically significant difference in ES FRR or MF FRR between the JMG, GBG, and BEG. However, all groups had a significant increase in ES FRR and MF FRR after the intervention. This suggests that all interventions had the same effect on the FRR. The results of this study indicate that the improvement in FRR was not due to an increase in activity measured during the active phase. The afferent changes during trunk flexion in patients with low back pain seemed to return to normal by the interventions in all three groups. The previous study showed that the low intensity, repetitive intervention method continued to stimulate group III and IV afferent neurons, resulting in a decrease in EMG activity.^{34,42,43} All intervention methods used by the three groups in this study were low intensity and repetitive. Thus, low intensity, repetitive programs

such as joint mobilization, gym ball exercises, and breathing exercises are thought to reset the sensitivity of the receptors over time and reduce the output contributing to the measured EMG activity at full thoracic flexion.^{8,44}

Adams et al⁸ reported that FRP is associated with pain, the mechanical load on the lumbar spine can lead to intervertebral disc rupture or fractures, and there is a strong association between spinal load and the prevalence of lumbar pain. FRP is a reaction of passive tissues such as ligaments or the fascia that support the FRP,¹⁰ and the FRP will disappear at the end of trunk flexion when feeling pain during exercise.^{10,31} Muscle pain alters the activity of the muscle spindle by stretching sensitivity and gamma-muscle spindle, impairing proprioception and detailed motor control.⁴⁵ Increased activity of afferent receptors in response to lumbar damage increases the firmness of the muscles to maintain the stability of the spine at locations where potentially impaired passive structures are mechanically damaged.^{46,47} Therefore, it can be inferred that the three 12-week intervention methods used in this study are effective in controlling pain. The FRR seems to be high in flexion relaxation. There were statistically significant differences in MVAS between the three groups in this study and post-hoc tests revealed that the GBG was significantly different from the JMG in the MVAS scores. The pain was significantly reduced in all groups after completion of the intervention. Joint mobilization may affect the neurophysiological and mechanical aspects such as pain, muscle defense, and muscle spasm, and it also can be used effectively to treat hypomobile or functionally fixed joints.^{48,49} Joint mobilization can stretch stiff tissue, increase joint motion range, facilitate normal movement of damaged joints, and prevent the symptoms from worsening by promoting nutrition. Proprioception sensation through joint movement precedes harmful stimulus recognition and then stimulates normal nerves to inhibit pain perception.⁵⁰ Stimulating the mechanical receptors of the joints by using joint mobilization can inhibit harmful stimulation at the spinal cord or brainstem level. Santilli et al⁵¹ found that joint mobilization is useful in the treatment of disk and nerve

damage. In this study, the pain decreased owing to increased joint motion range that restored normal mobility. Mechanical stimuli that move the joints are found to inhibit harmful stimuli that are transmitted to the spinal cord or the brain stem.^{51,52}

Gym ball exercises are often used to improve spinal stability and have been widely used in physical therapy for years. This exercise method is assumed to help reduce the risk of back pain.^{6,53} Gym ball exercises focus on maintaining the neutral spine and are suitable for targeting specific functions of local muscles in the early stages of programming to improve spinal stability. By maintaining the neutral position of the spine during gym ball exercises for as long as possible, the endurance of the trunk muscles can be improved. Improved trunk endurance can reduce the potential back pain.^{54,55} Gym ball exercises improved the stability and endurance of the spine and reduced pain in this study.

Previous randomized controlled studies of breathing exercises have shown that patients with an average of one year of moderate chronic back pain have significant improvement in both pain and functional symptoms after 8 weeks of breathing rehabilitation or physical therapy.²³ Diaphragm breathing, progressive muscle relaxation, exercise, self-visualization, and self-hypnosis have been shown to have effects in reducing stress and pain perception.⁵⁶ Intervention through measures such as relaxation and respiratory re-education is considered beneficial for chronic pelvic pain.²⁸ Holloway and West⁵⁷ suggest that breathing rehabilitation (Papworth Method) with a series of integrated breathing and relaxation exercises that focus on breathing pattern abnormalities (including hyperventilation) can improve quality of life. In addition, Park and Choi⁵⁸ suggest that lumbar stabilization exercises (back bride and hand-knee exercise) may counter asymmetry of the FRP in the erector spinae muscles, possibly preventing low back pain in the general population. In this study, breathing exercises improved various symptoms including lumbar pelvic pain and dysfunction and improved FRP and pain. However, further studies on breathing patterns are required.

A limitation of this study was the inability to control the strength and aerobic exercises during the experiment, and it was not possible to control the daily environment other than for the duration of the interventions. We could not apply all patients with chronic back pain who were recruited from a specific area or institution and who had chronic low back pain.

CONCLUSION

This study was conducted to investigate the effects of joint mobilization, gym ball exercises, and breathing exercises on the FRP and pain in patients with chronic low back pain. The results of this study indicate that breathing exercises can also improve FRP and pain in patients with chronic low back pain. Therefore, the results of this study indicate that breathing exercises can also improve FRP and pain in patients with chronic low back pain; therefore, breathing exercises could be actively considered for management of these patients.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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