Research Paper

Effects of Lumbar Stabilization and Graded Activity Exercises on Selected Biochemical Mediators and Clinical Outcomes in Patients With Non-specific Chronic Low Back Pain

Saturday Nicholas Oghumu[1, 2], Udoka Arinze Chris Okafor[3], Olumuyiwa Babalola Salu[4], Bosede Abidemi Tella[2],

1. Department of Physiotherapy, School of Postgraduate Studies, University of Lagos, Lagos, Nigeria.
2. Department of Physiotherapy, Faculty of Allied Medical Sciences, College of Medical Sciences, University of Calabar, Calabar, Nigeria.
3. Department of Physiotherapy, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria.
4. Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Lagos, Nigeria.

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ABSTRACT

Objectives: This study aims to investigate the effects of lumbar stabilization exercise (LSE) and graded activity exercise (GAE) on concentrations of interleukin (IL) 1A (IL1A), IL18 receptor 1 (IL18R1), IL18 receptor accessory protein (IL18RAP), IL-6, cyclooxygenase-2 (COX2), and clinical outcomes of pain intensity, disability, catastrophizing, diverting-attention, cognitive-coping and pain-reinterpretation in patients with non-specific chronic low back pain (NSCLBP).

Methods: This study was a single-blind parallel trial with an adaptive trial design. Fifty-four patients with NSCLBP were randomly assigned to LSE and GAE treatment groups. Demographic and anthropometric characteristics were measured. Treatments were administered twice a week for 10 weeks. The concentrations of IL1A, IL18R1, IL18RAP, IL-6, and COX2 of patients were assessed at four time points with enzyme-linked immunosorbent assay. Pain, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation were assessed at three time points with valid instruments. The responsiveness of the biochemical mediators to LSE and GAE was determined with a Bayesian one-way analysis of variance (ANOVA). Data were analyzed with descriptive and inferential statistics at $P<0.05$.

Results: The concentrations of IL1A, IL18R1, IL18RAP, and COX2 were unresponsive (Bayes factor [BF]<1) to LSE and GAE, while IL-6 concentrations were responsive (Bayes factor [BF]>1). The concentrations of IL-6 increased significantly ($P<0.05$) after LSE with a significant reduction ($P<0.05$) in pain, disability, and catastrophizing, while the concentration of IL-6 increased significantly ($P<0.05$) after GAE with a significant reduction ($P<0.05$) in pain, and disability. Effects of LSE and GAE on IL-6 concentrations, pain, and disability were comparable ($P>0.05$). Catastrophizing of patients with LSE was significantly less ($P<0.05$) compared to GAE.

Discussion: LSE increases IL-6 concentrations in NSCLBP patients while reducing pain, disability, and catastrophizing, while GAE increases IL-6 concentrations and reduces pain and disability. IL-6 concentrations, pain, and disability of patients were similar after LSE and GAE. Patients catastrophize less with LSE compared to GAE, hence LSE shows more beneficial effects for patients with NSCLBP than GAE.

*** Corresponding Author:**
Saturday Nicholas Oghumu, PhD.
Address: *Department of Physiotherapy, School of Postgraduate Studies, University of Lagos, Lagos, Nigeria.*
Tel: *+23 (48) 034215928*
E-mail: *nickyyivieosa@gmail.com.*

Highlights

- Lumbar stabilization exercise (LSE) increases interleukin (IL)-6 concentrations while reducing pain, disability, and catastrophizing in patients with non-specific chronic low back pain (NSCLBP).
- Graded activity exercise increases IL-6 concentrations while reducing pain and disability in patients with NSCLBP.
- Patients with NSCLBP had less catastrophizing with treatments of LSE than graded activity exercise

Plain Language Summary

This study sought to determine how lumbar stabilization and graded activity exercises (GAE), known to reduce pain and disability in patients with non-specific chronic low back pain (NSCLBP), affect concentrations of interleukin (IL) 1A (IL1A), interleukin18 receptor 1 (IL18R1), interleukin18 receptor accessory protein (IL18RAP), IL-6, cyclooxygenase-2 (COX2) and pain intensity, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation in patients with NSCLBP. The study showed that concentrations of IL1A, IL18R1, IL18RAP, and COX2 did not respond to lumbar stabilization and GAE, while IL-6 concentrations responded to lumbar stabilization and GAE. Also, the study showed that lumbar stabilization exercise (LSE) increases IL-6 concentrations in patients with NSCLBP while reducing pain, disability, and catastrophizing, while graded activity exercise increases IL-6 concentrations while reducing pain and disability. Both LSE and GAE have the same effect on IL-6 concentrations, pain, and disability. Patients' catastrophizing was reduced after LSE compared to graded activity exercise.

Introduction

Non-specific chronic low back pain (NSCLBP) represents the vast majority of chronic low back pain (CLBP) complaints consulted by physiotherapists [1]. It is defined as CLBP without a definite and recognizable primary disease, persisting for at least three months with clinical signs of muscle tension or stiffness localized below the costal margin of the spine and above the inferior gluteal folds in the presence or absence of sciatica [1]. The impact of NSCLBP on individuals and society is enormous because studies showed that it results in significant health burden, disability, absence from work, high cost of management, reduced quality of life, and increased psychological variables of anxiety with dissatisfaction and hopelessness [1-4].

Moreover, several treatment approaches for NSCLBP have evolved with differing principles at the centre of treatment algorithms [1, 2]. Therapeutic exercises are the first line of choice among different treatments for NSCLBP [1, 5]. Exercise therapy is effective for the management of NSCLBP resulting in improved clinical outcomes of pain, disability, and quality of life [1, 5, 6]. Also, among exercise therapies for NSCLBP, lumbar stabilization exercise (LSE) and graded activity exercises (GAE) are reported to be effective in reducing pain and disability [6]. LSE gained significant interest among CLBP researchers following the evidence that it activates the deep trunk muscles and restores synergic actions of the deep and superficial trunk muscles while reducing pain and disability in patients with NSCLBP [7, 8]. On the other hand, graded activity exercise addresses pain associated with fear of movement, unhelpful beliefs, and behavioral adaptations of NSCLBP while restoring dysfunctional muscle strength, endurance, and balance [9]. Interventionally, LSE emphasizes core stabilization using progressing strength and endurance exercises, while GAE uses behavioral quotas, pacing, and positive reinforcement as psychological constructs to enhance the muscle strength, endurance, and posture of patients with NSCLBP [9-11].

However, further studies on LSE and GAE in patients with NSCLBP are necessary because reports implicate numerous biochemical mediators in patients with NSCLBP [12-14]. Emerging evidence of pain mechanisms in NSCLBP suggests the need to profile biochemical mediators of pain for optimum intervention [3, 12]. Biochemically, the pain response is associated with the presence of inflammatory mediators of bradykinin, serotonin, histamine, adenosine triphosphate, prostaglandins, nitric oxides, cytokines, leukotrienes, cyclooxygenases, and neurotrophins [15]. Elevated levels of some biochemical mediators of pain have been reported in patients with NSCLBP [13, 16-18]. The cellular potentiation of some biochemical mediators is re-

ported to influence the persistence of chronic pain, such as NSCLBP [18]. Also, studies support the evaluation of biochemical mediators of interleukin (IL)-6, tumor necrosis factor-alpha, interleukin 1A (IL1A), interleukin 18 receptor 1 (IL18R1), interleukin 18 receptor accessory protein (IL18RAP), cyclooxygenase 2 (COX2) and matrix metalloprotease 3 given their association with disc degeneration, pain intensity, and disability in patients with NSCLBP [16, 17, 19, 20].

Consequently, evaluating biochemical mediators of pain as part of treatment outcome is desirable since recommendations are presented for favourable treatments in NSCLBP. When implemented as part of treatment outcome, the results from such studies help broaden and refine the clinical significance of recommended treatments. Along with issues of exercise superiority [21], few studies examine the effects of therapeutic exercises on biochemical mediators in patients with CLBP with promising results. The available evidence suggests the state of inducible immune activation after therapeutic exercises in patients with LBP [21-24]. Al-Obaidi and Mahmoud studied McKenzie's exercise on immune response in acute LBP [23], while Sokunbi et al. examined the effects of LSE on serotonin in CLBP [22]. Minobes-Molina et al. investigated the effect of multimodal treatments, including exercise therapies on IL-6 concentrations in NSCLBP [24]. Thus, few or no studies examine the effects of only therapeutic exercise on immune response in NSCLBP. Therefore, this study was designed to evaluate the effects of LSE and GAE on concentrations of IL1A, IL18R1, IL18RAP, IL6 COX2 and clinical outcomes of pain intensity, disability, catastrophizing, diverting attention, cognitive coping with pain reinterpretation in patients with NSCLBP. This study hypothesized that the effects of LSE and GAE on concentrations of selected cytokines and clinical outcomes are not significantly different.

Materials and Methods

Study design

The study was a single-blind parallel trial with an adaptive trial design. The study was registered with the Pan African Clinical Trial Registry. The trial was conducted in two phases, before which a feasibility study was conducted. Phase 1 obtained the baseline, age, and gender values of IL1A, IL18R1, IL18RAP, IL-6, and COX2 in patients with NSCLBP as reported by Oghumu et al. [25]. Also, phase 1 ascertained the responsiveness of IL1A, IL18R1, IL18RAP, IL-6, and COX2 to LSE and GAE for 10 weeks in patients with NSCLBP using an interim analysis. Phase 2 evaluated the effects of LSE and GAE on the responsive biochemical mediator (s) and the selected clinical outcomes in patients with NSCLBP.

Sampling technique and selection criteria

Consecutive sampling was used to recruit all participants. Participants' selection criteria were hinged on commonly reported domains for inclusion criteria in NSCLBP studies and the mean half-life of commonly used analgesics [26, 27]. The inclusion criteria included patients referred for only NSCLBP with or without radiating symptoms of at least three months, patients having no other site of pain, patients aged 18 to 60 years, and healthy individuals with no history of LBP in the last six months. The exclusion criteria included patients with a diagnosis of spinal inflammatory disease, such as ankylosing spondylitis, a history of spinal fracture or dislocation, motor or sensory deficit, pregnancy, any systemic or medical condition, such as diabetes, hematological disorder, acute or chronic liver diseases, autoimmune disease, use of oral or topical pain medications (non-steroidal anti-inflammatory drugs, steroid or any form of analgesics within the last two days before presentation), intention not to stop the analgesics during the study, a history of psychotropic medications, such as benzodiazepine, and open wound in any part of the body. Patients and healthy participants with a history of smoking and drinking alcohol in the last six months were excluded from the study.

Randomization, study groups, and blinding of participants

Patients with NSCLBP were randomly allocated to LSE and GAE by computer-generated block sizes varying between 4 and 8. Three groups existed in each phase of the trial. Group 1 was patients who received LSE, Group 2 was patients who received GAE, and Group 3 was healthy participants who received no treatment. Treatment appointments were scheduled for patients on different days to ensure blinding.

Determination of sample size

Oghumu et al. reported that in phase 1, 16 patients with NSCLBP and 16 healthy participants were calculated [25]. Each treatment group in phase 1 had 8 patients and 6 patients completed the treatments. For phase 2, Chan's formula (Equation 1) was used, which assumed a type 1 error and a power of 80% [28].

1. $n=c\times\pi_1(1-\pi_1)+\pi_2(1-\pi_2)/(\pi_1-\pi_2)^2$

Given a two-sided test of 5%, the formula assumes that a successful outcome of 25% in one intervention will only be relevant if we observe a 40% effect size of absolute improvement in the other intervention. Therefore, given that n=sample size, π_1=0.25, π_2=0.65, c depends on the power of the sample (c=7.9 for a power of 80%), n=7.9×0.25(1-0.25)+0.65(1-0.65)/(0.25-0.65)^2=21. For three groups, n=3×21=63. Assuming a 20% drop-out, n=63×1.25=78.75. Hence, 54 eligible patients with NSCLBP were randomly assigned to the treatment groups (Figure 1). Also, 27 volunteered healthy participants were recruited as control for baseline values.

Procedure for data collection

The same procedure was employed for the two phases of the trial. Participants' history and physical assessment were performed by the researcher to ascertain the inclusion and exclusion criteria. Then participants were given commencement dates for the study. On the first day of the participants' arrival, 8.5 mL of blood was drawn from their right arm by a phlebotomist into test tubes containing ethylenediaminetetraacetic acid as described by Vaught and Henderson [29]. All blood samples were taken at 11 AM. The test tubes were preserved at +4˚C in a container filled with cold packs and transported to a central research laboratory where the blood samples were processed and stored at -80˚C for analysis.

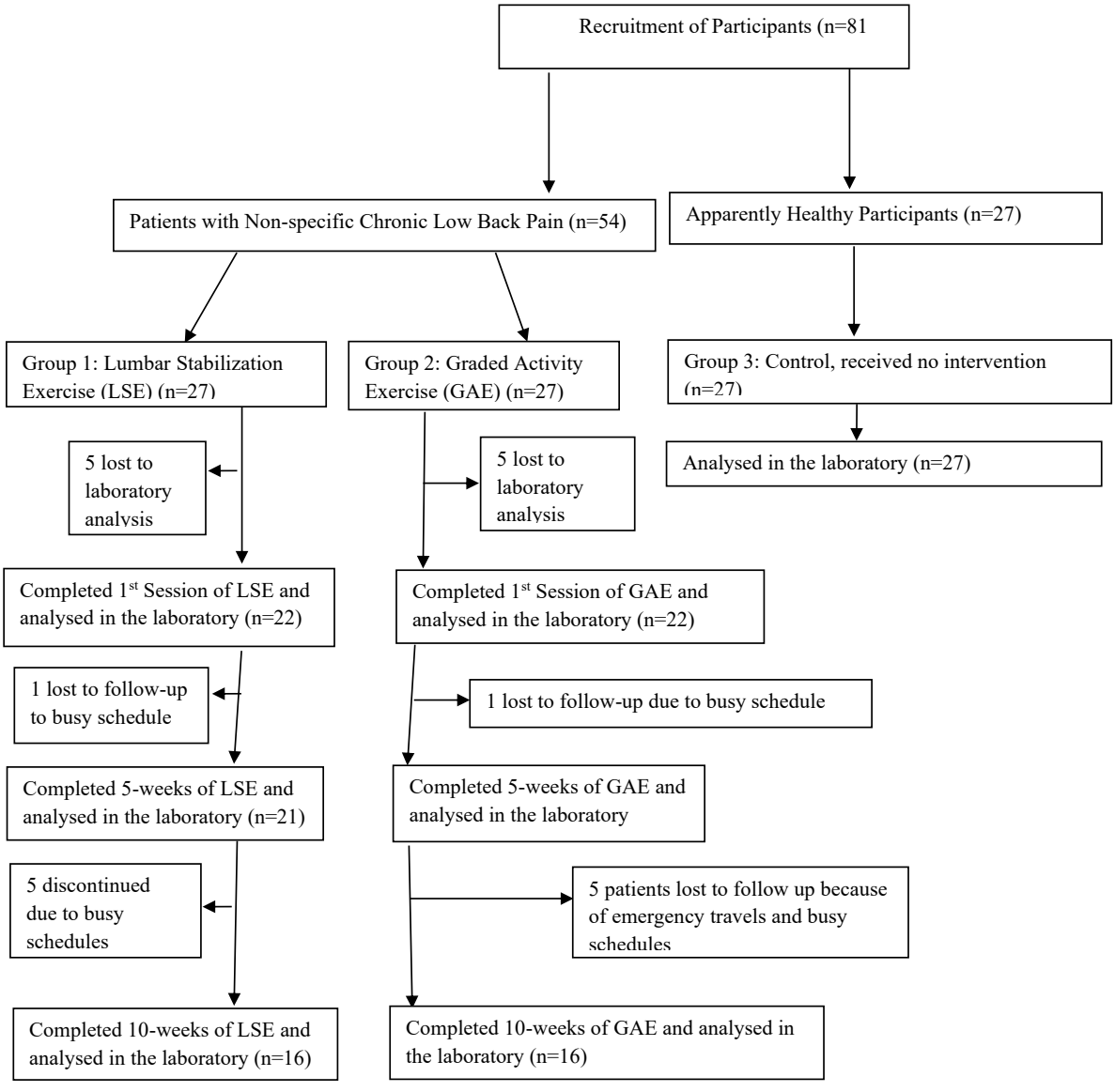

Figure 1. Treatment flow chart for phase two of the study

Participants' age and gender were obtained, heights were measured in meters (m) with the health-0-meter incorporated, Bridgeview, Illinois, United States of America, weights in kilograms (kg) with the Hana scale (model BR-9011-Germany), and percentage body fats in % with the Omron BF306 monitor. The body mass index (BMI) of participants was estimated in kg/m^2. Also, patients' clinical outcomes were assessed with the following instruments, pain intensity with a visual analogue scale (VAS), disability with a Roland Morris disability questionnaire 24 (RMDQ24), catastrophizing, diverting attention, cognitive coping, and pain reinterpretation with a coping strategy questionnaire 24 (CSQ24), respectively.

Treatments were administered two times a week for 10 weeks of 20 sessions. Post-treatment concentrations of IL1A, IL18R1, IL18RAP, IL-6, and COX2 were assessed on the first day, fifth and tenth weeks, respectively. Also, post-treatment pain intensity, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation were assessed in the fifth and tenth weeks, respectively.

Treatment procedures

The principles of exercise prescription were followed for LSE and GAE. Stretching exercises were performed before the LSE and GAE. Stretching was only indicated for observed tight muscles. A session of LSE or GAE lasted at least 45 minutes at three sets of repetitions. The abdominal drawing-in maneuver (Figure 2) was incorporated in all phases of the LSE, while cognitive behavioural therapy and bicycle ergometry were used in all phases of GAE (Figure 3). Phase 1 of the trial was conducted for 7 months, while phase 2 was conducted for 11 months.

Stretching exercises

Stretching exercises were performed on tight iliopsoas, rectus femoris, piriformis, and hamstrings of the lower extremities. Stretches were held for 30 s and repeated thrice.

Lumbar stabilization exercise (LSE)

LSE was based on the treatment program described in a previous study [30]. Three phases of the LSE program existed (Appendix). Phase 1 of the LSE was conducted for one session and it involved contraction of the transversus abdominis, multifidus, pelvic floor muscles, and diaphragm. It also involved isometric contraction of the erector spinalis and gluteus maximus in prone lying. Phase 2 LSE was conducted for 5 weeks and consisted of moderate-intensity (10 repetitions) closed-chain isometric strengthening of the gluteus maximus in prone, gluteus medius and minimus in side-lying, adductor magnus and brevis, iliopsoas in high sitting, quadriceps in supine and bridging exercise. It also involved strengthening exercises in functional position on all fours, full and semi-squatting, and proprioception training. Phase 3 of LSE was conducted for 5 weeks and consisted of high-intensity exercises (15 repetitions) in open-chain involving isometric strengthening of the same muscles in phase 2. It also involved isometric strengthening in open-chain functional positions on all fours, full and semi-squatting, and proprioception training.

Graded activity exercise (GAE)

GAE was based on the treatment program described by previous studies [9, 30]. The GAE aimed to increase patients' activity tolerance using individualized and sub-maximal exercises with cognitive behavioral principles, such as ignoring pain, pacing, explaining pain mechanisms, and reinforcing wellness behavior of exercise benefits. The individualized and sub-maximal exercises included isometric strengthening exercises to the quadriceps femoris, hamstring, gluteus maximus, gluteus medius and minimus, erector spinae, abdominal muscles, and bicycle ergometry (Appendix). The GAE was performed in three phases of sub-maximal exercises. Phases 1 and 2 were moderate-intensity exercises (10 repetitions) with 2 kg weights, while phase 3 consisted of high intensity (15 repetitions) with 3 kg weights. Phase 1 of the GAE lasted for one session, while phases 2 and 3 lasted for 5 weeks each.

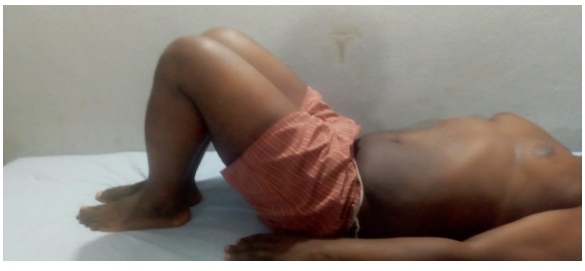

Figure 2. Abdominal drawing in manoever

Figure 3. Bicycle ergometry Iranian Rehabilitation Journal

Outcome measures

Visual analogue scale (VAS)

The VAS was represented by a 10 cm horizontal line. The horizontal line is anchored with no pain at one end and very extreme pain at the other end [31]. Patients were instructed to indicate their pain intensity by placing a vertical line on the horizontal line. The VAS is reported to have high reliability and validity scores [31].

Roland morris disability questionnaire 24 (RMDQ24)

The RMDQ24 has 24 items on physical functions likely to be affected by low back pain [32]. Its score involves adding up the number of items checked. The scores ranged from 0 (no disability) to 24 (maximum disability) [32]. The RMDQ24 has good construct validity with Cronbach's scores ranging from 0.7 to 0.90 [32].

Coping strategy questionnaire 24 (CSQ24)

The CSQ24 consists of 23 items about coping strategies [33]. It has a 7-point Likert scale ranging from "never do that" and "always do that," and one item measuring perceived control over pain with a 7-point Likert scale ranging from "no control" and "complete control [33]." It has four subscales, catastrophizing, diverting attention, reinterpreting, and cognitive coping. Each subscale is scored from zero to 36. The CSQ24 has a good level of validity [33].

Enzyme-linked immunosorbent assay (ELISA)

The ELISA was used to quantify the concentrations of IL1A, IL18R1, IL18RAP, IL-6, and COX2 in the collected blood samples, as described by Chiswick et al. [34]. The ELISA follows the same procedure, as described by Oghumu et al. [25] in phase 1 of the trial. The ELISA is very sensitive and valid to detect and measure proteins on the pictogram scale [35].

Data analysis

Data were analyzed using IBM SPSS software, Version 26. Data for concentrations of IL1A, IL18R1, IL-6, IL18RAP, and COX2 were log-transformed as recommended by the US center for disease control and prevention [36]. Descriptive statistics summarized the Mean±SD and percentages of the data. The Bayesian one-way repeated measure analysis of variance (ANOVA) was used to evaluate the responsiveness of the concentrations of IL1A, IL18R1, IL6, IL18RAP, and COX2 to LSE and GAE in phase 1 of the trial. The previously stated evidential categories of Bayes factor (BF_{10}) reported in the literature were used to inform the decision to respond [37].

Inferential statistics of Kruskal-Wallis one-way ANOVA tested the significant difference among study groups. The Mann-Whitney U test tested the significant difference in IL-6 concentrations between study groups. An independent t-test was used to test the significant difference in baseline values of clinical outcomes between treatment groups. The Friedman test determined the effects of LSE and GAE on patients' concentrations of IL-6. Also, the Wilcoxon test determined the within-group comparison of treatment effects of LSE and GAE on patients' concentrations of IL-6. One-way repeated measure ANOVA determined the treatment effects of LSE and GAE on patients' pain intensity, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation. The 95% CI was used for mean differences. The significance level was set at $P<0.05$.

Results

Sixteen patients with NSCLBP (56.25% men and 43.75% women) and 14 healthy individuals (50% men and 50% women) participated in phase 1 of the trial. Table 1 and Table 2 present the response of concentrations of IL1A, IL18R1, IL18RAP, IL-6, and COX2 to LSE and GAE in phase 1 of the trial, respectively. The result revealed that the concentrations of IL1A, IL18R1, IL18RAP, and COX2 were not responsive to LSE and GAE ($BF_{10}<1$) after 10 weeks of treatments, while the concentrations of IL-6 were responsive ($BF_{10}>1$) (Table 1 and Table 2). Hence, the trial on the effects of LSE and GAE on concentrations of IL1A, IL18R1, IL18RAP, and COX2 was stopped, while the trial on the effects of LSE and GAE on concentrations of IL-6 continued in phase 2.

A total of 54 patients with NSCLBP (42.59% men, 57.41% women) and 27 healthy individuals (55.56% men, 44.44% women) participated in phase 2 of the trial. The mean age, height, weight, BMI, pain intensity, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation of patients with NSCLBP were 49.54±7.80 years, 1.67±0.08 m, 73.65±11.77 kg, 26.41±3.81 kg/m^2, 6.22±1.82, 9.13±4.48, 15.11±9.16, 17.89±8.69, 9.22±7.37, 18.21±1.82, and 1.73±0.68 pg/mL, respectively (Table 3). Treatment groups (group 1 and 2) were comparable ($P>0.05$) in age, height, weight, BMI, percentage body fat, and baseline IL-6 concentrations, while patients in group 2 were significantly

Table 1. Response of selected biochemical mediators of pain to LSE using bayesian ANOVA (n=8, phase 1)

Variables		Mean±SD	Error	95% CI		
				Lower Bound	Upper Bound	B_{10}
IL1A (pg/mL)	Baseline	1.41±0.56	0.044	0.99	1.82	0.30
	After the 1st session	1.35±0.56	0.044	0.93	1.76	
	At 5 weeks	1.35±0.52	0.044	0.93	1.76	
	At 10 weeks	1.36±0.61	0.044	0.94	1.77	
IL18R1 (pg/mL)	Baseline	0.04±0.60	0.057	-0.43	0.50	0.10
	After the 1st session	-0.01±0.64	0.057	-0.48	0.46	
	At 5 weeks	-0.04±0.74	0.057	-0.51	0.43	
	At 10 weeks	0.06±0.55	0.057	-0.41	0.53	
IL18RAP (pg/mL)	Baseline	0.07±0.61	0.045	-0.34	0.49	0.09
	After the 1st session	0.10±0.58	0.045	-0.31	0.52	
	At 5 weeks	0.05±0.53	0.045	-0.37	0.47	
	At 10 weeks	0.06±0.55	0.045	-0.36	0.48	
IL6 (pg/mL)	Baseline	1.88±0.26	0.013	1.65	2.10	49.04
	After the 1st session	1.94±0.29	0.013	1.72	2.17	
	At 5 weeks	1.96±0.30	0.013	1.74	2.19	
	At 10 weeks	1.98±0.29	0.013	1.76	2.21	
COX2 (U/L)	Baseline	1.22±0.46	0.035	0.86	1.56	0.27
	After the 1st session	1.18±0.48	0.035	0.82	1.55	
	At 5 weeks	1.22±0.44	0.035	0.86	1.59	
	At 10 weeks	1.23±0.48	0.035	0.86	1.59	

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Abbreviations: IL1A: Interleukin 1-alpha; IL6: Interleukin-6; COX2: Cyclooxygenase-2; IL18R1: Interleukin-18 receptor 1; IL-RAP: Interleukin-18 receptor accessory protein; S^2: Variance; BF_{10}: Bayes factor testing alternate hypothesis versus null hypothesis; pg/mL: Picogram per milliliter; U/L: Unit per litre.

(P<0.05) higher in IL-6 concentration than the healthy participants (group 3) (Table 4 and Table 5). Also, treatment groups were comparable in baseline pain intensity, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation (P>0.05) (Table 6).

Furthermore, this study showed a statistically significant increase (P<0.05) in IL-6 concentration after 10 weeks of LSE and GAE in patients with NSCLBP (Table 7). The increase in IL-6 concentrations after LSE and GAE at 5 and 10 weeks, respectively, was statistically significant (P<0.05) (Table 8). Also, this study showed a statistically significant decrease (P<0.05) in pain intensity, disability, and catastrophizing in patients with NSCLBP after 10 weeks of LSE, while diverting attention, cognitive coping, and reinterpretation of pain were comparable (P>0.05) (Table 9). On the other hand, this study showed a statistically significant decrease (P<0.05) in pain intensity and disability in patients with NSCLBP after 10 weeks of GAE, while diverting attention, catastrophizing, cognitive coping, and reinterpretation of pain were comparable (P>0.05) (Table 10). The decrease in pain intensity, disability, and catastrophizing was statistically significant (P<0.05) at 5 and 10 weeks

Table 2. Response of selected biochemical mediators of pain to graded activity exercise using bayesian one-way repeated measure analysis of variance (n=8, phase 1)

Variables		Mean±SD	Error	95% CI		BF_{10}
				Lower Bound	Upper Bound	
IL1A (pg/mL)	Baseline	1.55±0.72	0.017	1.30	1.81	0.14
	After the 1st session	1.54±0.57	0.017	1.29	1.80	
	At 5 weeks	1.50±0.69	0.017	1.25	1.76	
	At 10 weeks	1.55±0.78	0.017	1.30	1.81	
IL18R1 (pg/mL)	Baseline	0.30±0.79	0.021	0.02	0.59	0.46
	After the 1st session	0.32±0.84	0.021	0.04	0.61	
	At 5 weeks	0.29±0.67	0.021	0.01	0.58	
	At 10 weeks	0.37±0.82	0.021	0.08	0.65	
IL18RAP (pg/mL)	Baseline	0.21±0.77	0.020	-0.07	0.49	0.08
	After the 1st session	0.26±0.77	0.020	-0.02	0.54	
	At 5 weeks	0.25±0.77	0.020	-0.03	0.53	
	At 10 weeks	0.25±0.75	0.020	-0.03	0.53	
IL6 (pg/mL)	Baseline	2.22±0.48	0.008	2.05	2.40	22.11
	After the 1st session	2.19±0.49	0.008	2.01	2.36	
	At 5 weeks	2.29±0.46	0.008	2.12	2.47	
	At 10 weeks	2.21±0.52	0.008	2.03	2.38	
COX2 (U/L)	Baseline	1.52±1.65	0.096	0.92	2.13	0.12
	After the 1st session	1.46±1.62	0.096	0.86	2.07	
	At 5 weeks	1.51±1.60	0.096	0.90	2.11	
	At 10 weeks	1.50±1.76	0.096	0.89	2.11	

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Abbreviations: IL1A: Interleukin 1-alpha; IL6: Interleukin-6; COX2: Cyclooxygenase-2; IL18R1: Interleukin-18 receptor 1; IL-RAP: Interleukin-18 receptor accessory protein; S^2: Variance; BF_{10}: Bayes factor testing alternate hypothesis versus null hypothesis; pg/mL: Picogram per milliliter; U/L: Unit per litre.

of LSE, while the decrease in pain intensity, and disability after GAE was statistically significant (P<0.05) at 10 weeks only (Table 11). LSE and GAE were comparable (P>0.05) in IL-6 concentrations (Table 12). Also, LSE and GAE were comparable (P>0.05) in patients' pain intensity, disability, diverting attention, cognitive coping, and pain reinterpretation with the difference that patients' ability to catastrophize was significantly decreased (P<0.05) at 5 and 10 weeks of LSE compared to GAE (Table 13).

Discussion

This study evaluated the effects of LSE and GAE on concentrations of IL1A, IL18R1, IL18RAP, IL-6, COX2 and pain intensity, disability, catastrophizing, diverting attention, cognitive coping, and pain reinterpretation in patients with NSCLBP. Phase 1 of the trial determined the responsiveness of concentrations of IL1A, IL18R1, IL18RAP, IL-6, and COX2 to LSE and GAE for 10 weeks. It was found that only the concentration of IL-6 was responsive to LSE and GAE, while concentra-

Table 3. Physical characteristics of patients with NSCLBP and healthy participants (phase 2)

Variables		Mean±SD	Min	Max
Patients participants (n=54)	Age (y)	49.54±7.80	35.00	60.00
	Height (m)	1.67±0.08	1.50	1.88
	Weight (kg)	73.65±11.77	56.00	96.90
	BMI (kg/m²)	26.41±3.81	19.38	38.44
	PBF (%)	27.10±9.76	6.70	46.30
	Pain intensity	6.22±1.82	3.00	10.00
	Disability	9.13±4.48	1.00	22.00
	Catastrophizing	15.11±9.16	0.00	30.00
	Diverting attention	17.89±8.69	0.00	36.00
	Cognitive coping	9.22±7.37	0.00	33.00
	Pain reinterpretation	18.21±1.82	0.00	30.00
	Interleukin 6 (pg/mL)	1.73±0.68	0.11	3.21
Healthy participants (n=27)	Age (y)	46.48±6.10	34.00	55.00
	Height (m)	1.64±0.06	1.53	1.76
	Weight (Kg)	67.18±8.24	51.00	81.00
	BMI (kg/m²)	24.98±3.30	18.07	30.50
	PBF (%)	23.98±8.66	8.50	35.20
	Interleukin 6 (pg/mL)	1.03±1.16	0.00	2.90

Abbreviations: BMI: Body mass index; PBF: Percentage body fat; pg/mL: Picogram per milliliter.

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tions of IL1A, IL18R1, IL18RAP, and COX2 were not responsive to LSE and GAE for 10 weeks. Hence, the trial on the effects of LSE and GAE on concentrations of IL1A, IL18R1, IL18RAP, and COX2 was stopped after phase 1, while the trial on the effects of LSE and GAE on concentrations of IL-6 continued in phase 2. For pain biomarker studies, Bayes' theorem provides a useful guide for new studies because not all pain biomarkers may have predictive value [38]. Therefore, it is advisable to conduct an interim analysis for biomarkers in a prospective study, especially when limited data support such biomarkers.

The results of this study regarding patients' mean age of 49.54 years are consistent with the reports that the prevalence of low back pain peaks between the mid-30s and mid-50s [39]. A similar result was reported in phase 2 with a significant concentration of IL-6 in the patients than healthy individuals in phase 1 of the study [25]. One argument in support of higher concentrations of IL-6 in patients with NSCLBP than in healthy control is its pro-inflammatory and anti-inflammatory roles in disease conditions [40, 41].

IL-6 concentrations increased after 10 weeks of LSE and GAE. The result of increased IL-6 concentration after 10 weeks of LSE is in contrast to the report of Capossela et al. [42]. Capossela et al. reported lower concentrations of IL-6 in patients with CLBP after long-term conservative treatments; although, the physiotherapy components of the conservative management were not classified [42]. Nevertheless, this result of increased IL-6 concentration in this present study is consistent with the report of increased levels of IL-6 following exercise [24, 40, 43, 44]. Legard and Pederson assert that IL-6 is mainly produced and released by contracting skeletal

Table 4. Baseline comparison of participants physical characteristics among study groups using Kruskal-Wallis ANOVA (n=81, Phase 2)

Variables	Mean Rank Groups*			H	df	Asymptotic Sig.
	1	2	3			
Age (y)	45.28	42.81	34.91	2.87	2	0.238
Height (m)	47.41	41.35	34.24	4.26	2	0.119
Weight (kg)	47.78	42.02	33.20	5.26	2	0.072
BMI (kg/m^2)	44.52	40.89	37.59	1.17	2	0.557
PBF (%)	44.04	43.00	35.96	1.88	2	0.390
IL6 (pg/mL)	39.41	43.48	28.33	7.00	2	0.030***

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Abbreviations: IL6: Interleukin-6; pg/mL: Picogram per millilitre BMI: Body mass index; PBF: Percentage body fat.

Group 1: Participants who received lumbar stabilization exercise; Group 2: Participants who received graded activity exercise; Group 3: Healthy participants who received no intervention.

*n=27 in each group, ***Significance.

Table 5. Pair-wise analysis of baseline IL-6 concentration among study groups using Mann Whitney U Test (phase 2)

Variables		MR vs MR	SR v. SR	Z	Asymptotic Sig.
Interleukin 6 (pg/mL)	Group 1 vs group 2	21.63 vs 24.43	497.50 vs 437.50	-0.71	0.474
	Group 1 vs group 3	29.78 vs 21.85	685.00 vs 590.00	-1.92	0.055
	Group 2 vs group 3	30.55 vs 20.48	672.00 vs 553.00	-2.45	0.014***

Abbreviations: MR: Mean rank; SR: Sum of rank; pg/mL: Picogram per milliliter.

Group 1: Patients who received lumbar stabilization exercise; Group 2: Patients who received graded activity exercise; Group 3: Healthy participants who served as the control group.

***Significant P<0.05.

Table 6. Baseline comparison of clinical outcome measures between treatment groups using levene's test of homogeneity (phase 2)

Variables	Mean±SD		F	P
	Group 1 (n=27)	Group 2 (n=27)		
Pain intensity	5.39±1.46	8.02±5.36	1.4	0.290
Disability	8.56±3.87	9.70±5.03	0.2	0.840
Catastrophizing	10.48±7.27	9.81±7.17	0.1	0.890
Diverting attention	16.59±6.69	19.18±10.27	0.1	0.880
Cognitive coping	7.70±6.30	10.74±8.14	0.0	0.490
Pain reinterpretation	16.81±9.88	19.61±9.26	0.1	0.390

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Group 1: Patients who received lumbar stabilization exercise; Group 2: Patients who received graded activity exercise.

Table 7. Treatment effects of LSE and GAE on IL-6 concentrations of patients with non-specific chronic low back pain using Friedman test (phase 2)

Variables		Mean Rank	Mean±SD	df	χ^2	Asymptotic Significance
Group 1 (LSE)	Baseline IL6	1.75	1.64±0.59	3	12.97	0.005***
	IL6 After the 1st session	2.11	1.68±0.67			
	IL6 at 5 weeks	2.79	2.00±0.54			
	IL6 at 10 weeks	3.36	2.14±0.41			
Group 2 (GAE)	Baseline IL6	1.50	1.60±0.66	3	15.51	0.001***
	IL6 After the 1st session	2.29	1.93±0.63			
	IL6 at 5 weeks	3.29	2.15±0.56			
	IL6 at 10 weeks	2.93	2.25±0.44			

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Abbreviations: SD: Standard deviation; χ^2: Chi-square; LSE: Lumbar stabilization exercise; GAE: Graded activity exercise; IL6: Interleukin 6; pg/mL: Picogram per milliliter.

***Significant at P≤0.05.

muscles, and IL-6 increases exponentially in proportion to the length of exercise and the amount of muscle mass engaged in the exercise [43]. Likewise, increased IL-6 concentration was reported after drug therapy involving tocilizumab for lumbar pain [45].

In this regard, Minobes-Molina et al. found that LSE increases IL-6 concentrations in patients with NSCLBP [24]. However, Minobes-Molina et al. reported that traditional exercise therapy decreases IL-6 in patients with NSCLBP [24]. However, it is worth noting that the interventional approach of this present study differs from that

Table 8. Pair-wise comparison of treatment effects of LSE and GAE on IL-6 concentrations using wilcoxon test (phase 2)

Variables		MR	SR	Z	Asymptotic Significance
Lumbar stabilization exercise	Baseline vs the 1st session	11.33	19.00	-1.38	0.167
	Baseline vs at 5 weeks	7.75	24.00	-2.58	0.010***
	Baseline vs at 10 weeks	9.00	15.00	-2.38	0.017***
	The 1st session vs at 5 weeks	7.25	18.00	-2.46	0.014***
	The 1st session vs at 10 weeks	6.33	14.00	-2.33	0.020***
	At 5 weeks vs at 10 weeks	11.33	11.00	-0.40	0.687
Graded activity exercise	Baseline vs the 1st session	12.60	126.00	-0.02	0.987
	Baseline vs at 5 weeks	5.50	11.00	-3.38	0.001***
	Baseline vs at 10 weeks	1.50	3.00	-3.11	0.002***
	The 1st session vs at 5 weeks	9.29	65.00	-1.78	0.079
	The 1st session vs at 10 weeks	7.25	29.00	-2.02	0.044***
	At 5 weeks vs at 10 weeks	6.11	55.00	-0.67	0.501

MR: Mean rank; SR: Sum of rank.

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***Significant P<0.05.

Table 9. Treatment effects of LSE on clinical outcome measures of patients with NSCLBP using one-way repeated measure ANOVA (phase 2)

Variables		Mean±SD	SS	df	MS	F	Partial η^2	P
Pain intensity	Baseline	5.34±1.13	157.67	2	103.48	78.39	0.80	0.000***
	At 5 weeks	2.87±1.36						
	At 10 weeks	1.41±1.05						
Disability	Baseline	9.15±3.77	450.01	2	284.37	52.61	0.74	0.000***
	At 5 weeks	5.50±2.96						
	At 10 weeks	2.45±2.45						
Catastrophizing	Baseline	23.35±4.36	2099.73	2	1452.47	317.64	0.94	0.000***
	At 5 weeks	14.75±3.48						
	At 10 weeks	8.95±2.33						
Diverting attention	Baseline	16.75±7.25	84.23	2	44.22	0.72	0.04	0.486
	At 5 weeks	14.40±7.54						
	At 10 weeks	17.05±12.59						
Cognitive coping	Baseline	8.55±6.15	102.70	2	72.82	0.83	0.04	0.408
	At 5 weeks	11.30±7.76						
	At 10 weeks	11.35±11.13						
Reinterpretation	Baseline	18.55±9.49	90.13	2	53.86	0.61	0.03	0.523
	At 5 weeks	19.95±9.52						
	At 10 weeks	21.55±10.41						

Abbreviations: SS: Sum of squares; MS: Mean square; SD: Standard deviation.

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***Significant at P<0.05.

of Minobes-Molina et al. The present study administered only exercise therapies (LSE and GAE), while Minobes-Molina et al. used a multimodal approach, including transcutaneous electrical nerve stimulation, infrared therapy, and exercise therapies [24]. Also, exercise therapies in Minobes-Molina et al. were administered with moderate intensities (10 repetitions), while exercise therapies in this present study were administered with moderate and high intensities (10 and 15 repetitions) [24].

Even though IL-6 is a pro-inflammatory cytokine, studies have shown that the contracting skeletal muscle can produce IL-6 to mediate anti-inflammation [24, 40, 43, 46]. IL-6 has two signaling pathways termed trans-signaling and classic signaling [41]. IL-6 trans-signaling mediates pro-inflammatory effect, while IL-6 classical signaling mediates anti-inflammation and regenerative effects [41]. Classical signaling of IL-6 occurs through the activation of cell membrane-bound IL-6 receptors [41]. Thus, it can be concluded that the higher concentration of IL-6 observed in patients with NSCLBP at baseline in this study may be due to the pro-inflammatory effects of IL-6, while the increase in IL-6 concentrations after LSE and GAE in patients with NSCLBP may be due to the anti-inflammatory effects of IL-6 activated by the contraction of the skeletal muscles.

In summary, IL-6 is reported to mediate anti-inflammatory effects and plays a role in myogenesis in a classical signaling phenomenon [24, 40, 41, 43]. Collaboratively, LSE and GAE are reported to alleviate pain and increase muscle strength in patients with NSCLBP [6-11, 30]. Thus, the result of this study on increased IL-6 concentration after LSE and GAE may help to explain

Table 10. Treatment effects of graded activity exercise on clinical outcomes of patients with NSCLBP using one-way repeated measure ANOVA (phase 2)

Variables		Mean±SD	SS	df	MS	F	Partial η^2	P
Pain intensity	Baseline	8.44±6.43	228.33	2	198.73	8.94	0.34	0.006***
	At 5 weeks	4.58±2.13						
	At 10 weeks	3.70±5.65						
Disability	Baseline	10.67±5.36	237.60	2	151.04	10.04	0.37	0.001***
	At 5 weeks	8.57±5.82						
	At 10 weeks	5.56±4.58						
Catastrophizing	Baseline	10.78±7.79	25.04	2	16.77	0.44	0.02	0.594
	At 5 weeks	9.33±6.22						
	At 10 weeks	9.33±8.58						
Diverting attention	Baseline	20.78±11.21	72.48	2	38.57	0.72	0.04	0.485
	At 5 weeks	22.06±10.18						
	At 10 weeks	19.22±10.87						
Cognitive coping	Baseline	11.67±8.64	202.16	2	106.91	1.88	0.10	0.171
	At 5 weeks	14.72±8.27						
	At 10 weeks	16.33±9.30						
Reinterpretation	Baseline	18.63±10.66	57.92	2	38.42	0.60	0.03	0.512
	At 5 weeks	21.17±8.72						
	At 10 weeks	19.78±8.82						

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Abbreviations: SS: Sum of squares; MS: Mean square; SD: Standard deviation; ANOVA: Analysis of variance.

***Significant at P<0.05.

the biochemical means of LSE and GAE to reduce pain intensity in patients with NSCLBP.

However, the effects of LSE and GAE on IL-6 concentrations were not significantly different in this study. This result that no significant difference is observed in IL-6 concentration between LSE and GAE in patients with NSCLBP is consistent with Legard and Pederson's report [43]. Legard and Pederson opined that exercise-induced levels of cytokines depend on the intensity, mode, and frequency of the exercise [43]. Given that the 5 and 10 weeks of LSE and GAE differed in intensity and mode but not frequency, it is reasonable to imply that the exercise factor of frequency may be a crucial indicator for IL-6 response to exercise. In other words, the effects of LSE and GAE of different modes and intensities but with the same frequency on IL-6 concentrations in patients with NSCLBP are not significantly different. Sokunbi et al. found no significant difference between the two modes of exercise but found a significant difference between exercise frequencies in serotonin concentration in patients with CLBP [23].

Again, the results of this study on reduced pain intensity and disability after LSE and GAE are consistent with the reports of previous studies [6-11, 30]. These results of reduction in pain intensity and disability after LSE and GAE imply that both LSE and GAE are effective in reducing pain and disability in patients with NSCLBP. However, LSE had a better therapeutic outlook than GAE because patient catastrophizing was significantly reduced only after 10 weeks of LSE. Harland

Table 11. Bonferroni post hoc test of clinical outcome measures after LSE and GAE in patients with NSCLBP (phase 2)

Variables		Test Variable (I)	Testing Variable (J)	MD (I-J)	P
Group 1 (LSE)	Pain intensity	Baseline	After 5 weeks	2.47	0.000***
			After 10 weeks	3.93	0.000***
		At 5 weeks	Baseline	-2.47	0.000***
			After 10 weeks	1.46	0.000***
		At 10 weeks	Baseline	-3.93	0.000***
			After 5 weeks	-1.46	0.000***
	Disability level	Baseline	After 5 weeks	3.65	0.000***
			After 10 weeks	6.70	0.000***
		At 5 weeks	Baseline	-3.65	0.000***
			After 10 weeks	3.05	0.000***
		At 10 weeks	Baseline	-6.70	0.000***
			After 5 weeks	-3.05	0.000***
	Catastrophizing	Baseline	After 5 weeks	8.60	0.000***
			After 10 weeks	14.40	0.000***
		At 5 weeks	Baseline	-8.60	0.000***
			After 10 weeks	5.80	0.011***
		At 10 weeks	Baseline	-14.40	0.000***
			After 5 weeks	-5.80	0.011***
Group 2 (GAE)	Pain intensity	Baseline	After 5 weeks	3.85	0.063
			After 10 weeks	4.74	0.000***
		At 5 weeks	Baseline	-3.85	0.063
			After 10 weeks	0.88	1.000
		At 10 weeks	Baseline	4.74	0.000***
			After 5 weeks	-0.88	1.000
	Disability level	Baseline	After 5 weeks	2.10	0.393
			After 10 weeks	5.11	0.000***
		At 5 weeks	Baseline	-2.10	0.393
			After 10 weeks	3.01	0.082
		At 10 weeks	Baseline	-5.11	0.000***
			After 5 weeks	-3.01	0.082

Abbreviations: MD: Mean difference; LSE: Lumbar stabilization exercise; GAE: Graded activity exercise. Iranian Rehabilitation Journal

***Significant at P<0.05.

Table 12. Comparative effects of LSE and GAE on IL-6 concentrations in patients with NSCLBP using Mann-Whitney U test (phase 2)

Variables		Mean Rank		Z	P
		Group 1 (LSE)	Group 2 (GAE)		
At 5 weeks	IL6 (pg/mL)	22.38	20.62	-0.46	0.642
At 10 weeks	IL6 (pg/mL)	16.15	17.91	-0.52	0.601

Abbreviations: LSE: Lumbar stabilization exercise; GAE: Graded activity exercise; IL6: Interleukin 6; pg/mL: Picogram per millilitre.

Table 13. Comparative effects of LSE and GAE on clinical outcomes in patients with NSCLBP using independent t-test (phase 2)

Variables		Mean±SD		t	F	P
		Group 1 (LSE)	Group 2 (GAE)			
At 5-weeks	Pain intensity	2.8±1.94	4.02±6.11	-0.89	1.44	0.378
	Disability	4.09±3.04	2.54±5.50	1.14	1.72	0.259
	Catastrophizing	-6.09±4.65	-1.20±6.79	2.74	2.11	0.009***
	Diverting attention	1.54±9.46	1.00±10.44	0.81	0.00	0.421
	Cognitive coping	2.77±8.29	2.70±11.10	-0.03	3.22	0.979
	Reinterpretation	1.95±10.11	2.63±10.63	0.21	0.00	0.834
At 10-weeks	Pain intensity	3.93±1.46	4.74±2.09	-1.39	0.20	0.173
	Disability	6.70±3.64	5.11±3.39	1.39	0.01	0.173
	Catastrophizing	-7.60±4.58	-1.44±9.49	2.59	6.56	0.014***
	Diverting attention	0.30±11.50	1.56±8.74	-0.56	0.41	0.582
	Cognitive coping	2.80±10.02	1.95±10.11	0.46	2.15	0.646
	Reinterpretation	3.00±14.57	1.15±11.11	-0.44	0.49	0.665

LSE: Lumbar stabilization exercise; GAE: Graded activity exercise.

***Significant at P≤0.05.

and Martins reported that variability in catastrophizing scores over time is one of the factors suggesting effective treatment [47]. Also, this deduction of a more beneficial effect of LSE than GAE is buttressed by the result of this present study that the patient's ability to catastrophize was significantly lower in LSE compared to GAE. Previous studies have highlighted the prognostic indication of pain catastrophizing in CLBP management [48, 49]. LSE may be more beneficial than GAE for treating patients with NSCLBP because LSE reduces catastrophizing in addition to reducing pain and disability in patients with NSCLBP.

Conclusion

LSE increases IL-6 concentrations in patients with NSCLBP while reducing pain, disability, and catastrophizing, while GAE increases IL-6 concentrations while reducing pain, and disability in patients with NSCLBP. Patients' concentrations of IL1A, IL18R1, IL18RAP, and COX2 were not responsive to LSE and GAE. Both LSE and GAE were similar in effects on IL-6 concentrations, pain, and disability in patients with NSCLBP. Patients catastrophize less with LSE compared to GAE, hence suggesting more beneficial effects of LSE for patients with NSCLBP than GAE.

Strengths and weakness of this study

This study provides the clinical implications of LSE and GAE administration on the concentrations of IL1A, IL18R1, IL18RAP, IL-6, and COX2 in patients with NSCLBP. The results of this study may be useful as an objective means for clinicians and patients to evaluate the biochemical effects of LSE and GAE administrations in patients with NSCLBP. One limitation of this study is that little literature relatively supports the evaluation of the selected biochemical mediators in patients with NSCLBP for therapeutic exercises in clinical settings. Another limitation was that the investigators were unaware of the need to evaluate membrane-bound IL-6 receptors as part of the selected biochemical mediators given that IL-6 anti-inflammatory and myogenic roles rely on classical signaling through the membrane-bound IL-6 receptor. Hence, IL-6 responses to LSE and GAE in this study were interpreted by the effects of LSE and GAE on pain intensity and disability in patients with NSCLBP.

Ethical Considerations

Compliance with ethical guidelines

Ethical approval was obtained from the Health Research and Ethics Committee of an Academic Teaching Hospital (Code: ADM/DCST/HREC/APP/2638), National Orthopaedic Hospital, (Code: OH/90/C/IX), and a General Hospital (Code: LSHSC/2222/VOL.X/205). Also, participants' consent was sought and obtained.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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Appendix

A. Lumbar stabilization exercise-richardson approach intervention manual

Exercise program for LSE were slated for duration of at least 45 minutes and were performed twice a week. In all, the exercises were performed three sets of 10 repetitions for phases 1 and 2, and three sets of 15 repetition for phase 3. The exercise program goals were to: Retrain the motor control and ability of the deep muscles of the lumbopelvic region (specifically transversus abdominis, inferior fibres of the internal oblique multifidus, Diaphragm and the pelvic floor muscles); re-educate motor control of the superficial muscles of the lumbopelvic region (specifically external oblique, rectus abdominis, erector spinae; encourage postures and patterns of movement that reduces pain; retrain coordination between deep and superficial muscles of the lumbopelvic region during static and dynamic tasks; retrain breath control with trunk motor control strategies; progress training for function. There were three phases of the LSE program. To progress from phase one to phase two, the basic requirements were co-contraction of the muscles of the local synergy in supine, prone, side lying, sitting and standing. The phase two LSE program consisted of moderate intensity exercises with closed-chain segmental control. Progression was through increased repetition (10 repetitions), holding times of 10 counts for endurance and movement of the limb(s) through full excursion. The phase three LSE program consisted of high intensity exercises with open-chain segmental control. Progression was through increased repetition (15 repetitions), increased holding times (20 counts for endurance) and movement of the limb(s) through full excursion.

Phases of lumbar stabilization exercise

Phase one: Local segmental control

(i) Activation of the deep back muscles (abdominal hollowing)

Indication: To strengthen the transversus abdominis, multifidus and pelvic floor muscles

Position: Supine with both knees flexed to 90°.

Method: The patient was instructed to breathe in and as he/she exhales, he/she slowly draws in the abdomen to flatten it without using the chest (Plate 1).

The patient is allowed several repetitions to optimize the performance of the contraction in phase 1. The goal was to hold the contraction for 10s and repeat the contraction 10 times.

Repetition: 10 repetitions of transverse abdominis contraction

Duration: 5 minutes

Frequency: 3 set of 10 repetitions

Sessions: one

(ii) Activation of the superficial back muscles

Indication: To strengthen gluteus maximus and also to relax the hyperactive global back muscles.

Position: Prone lying

Procedure: The researcher instructed the patient to lift one arm and the opposite leg and hold both for 10 seconds (Plate 2). Thereafter, repeat for the alternate arm and leg.

Plate 1. Activation of the deep back muscles (abdominal hollowing)

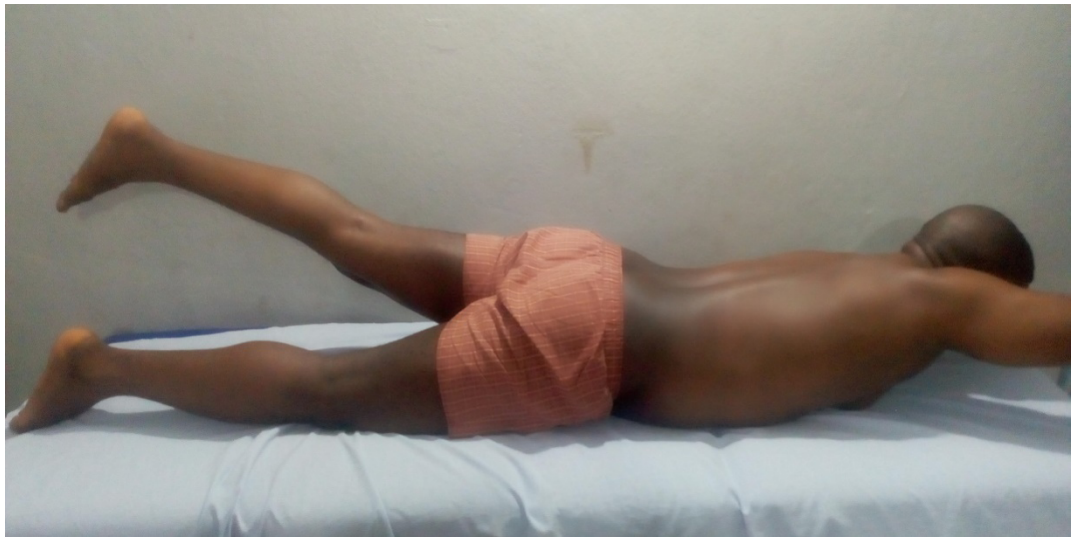

Plate 2. Activation of the superficial back muscles

Repetition: 10 times for each alternate arm and leg

Duration: 10 minutes

Frequency: 3 set of 10 repetitions

Sessions: one

Phase two: Moderate intensity with closed-chain segmental control

This involved incorporating the activation of the deep back muscles (abdominal hollowing) in the following:

(i) Isometric holding of the gluteus maximus

Indication: To strengthen gluteus maximus

Position: Prone lying

Procedure: With one a thera-band wrapped round ankle on the couch, the researcher instructed the patient to lift one of the lower extremities up holding for 10 seconds (Plate 3). Thereafter, repeat for the other leg.

Repetition: 10 times for each leg

Duration: 10 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(ii) Isometric holding of the gluteus medius and gluteus minimus muscles

Indication: To strengthen the gluteus medius

Position: Side lying

Procedure: Participant was instructed to lie on the side and a thera-band was wrapped around the ankles; the researcher then instructed the patient to abduct the lower extremity on top as much as possible holding for 10 seconds (Plate 4).

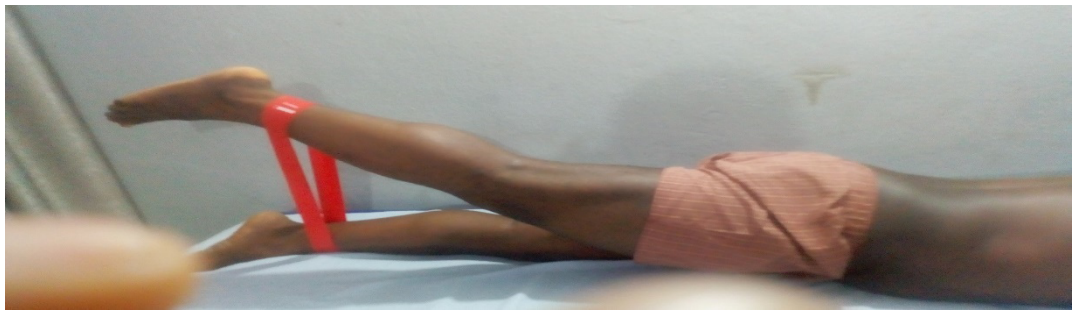

Plate 3. Isometric holding of the gluteus maximus in prone

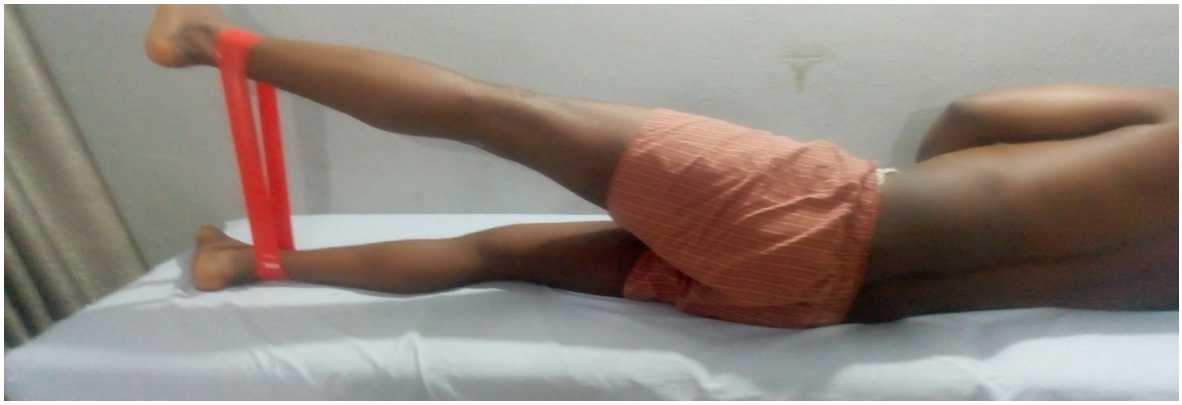

Plate 4. Isometric holding of the gluteus medius and gluteus minimus muscles

Repetition: 10 times for each leg

Duration: 10 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(iii) Isometric holding of the adductor magnus and brevis

Indication: To strengthen adductor magnus and brevis

Position: Side lying

Procedure: With the patient lying in side lying with one lower extremity crossing fully on the other and thera-band wrapped around the ankle, the researcher instructed the patient to lift the other lower extremity up holding both for 10 seconds (Plate 5). Thereafter, repeat for the other leg.

Repetition: 10 times for each leg

Duration: 10 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(iv) Isometric holding of the iliopsoas

Indication: To strengthen the iliopsoas

Position: High sitting with thera-band wrapped round the distal thigh

Procedure: The researcher instructed the patient to lift the thigh of one lower extremity with the other thigh on the couch, hold for 10 seconds (Palte 6). Thereafter, repeat for the other lower extremity.

Repetition: 10 times for each leg

Duration: 10 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(v) Isometric bridging exercises

Plate 5. Isometric holding of the adductor magnus and brevis

Figure 6. Isometric holding of the iliopsoas

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Indication: To strengthen the gluteus maximus and erector spinae

Position: Supine lying with the knees bent to 90°.

Procedure: The researcher instructed the patient to lift the buttocks up and hold for 10 seconds (Palte 7).

Repetition: 10 times for each leg

Duration: 5 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(vi) Isometric holding of the quadriceps

Indication: To strengthen the quadriceps femoris

Position: Supine lying with thera-band wrapped around the ankle

Procedure: The researcher instructed the patient to lift one leg with the other leg on the couch and hold for 10 seconds (Plate 8). Then repeat for the other leg.

Repetition: 10 times for each leg

Duration: 10 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(vii) Stabilization in quadruple position

Indication: Activation of the deep back muscles in quadruple position for lumbopelvic stability

Position: Kneeling with both hands standing on the couch (on all fours)

Procedure: The researcher instructed the patient to go into kneeling position such that the hip and knees were flexed and both hands standing on the couch while incorporating abdominal hollowing holding for 10 seconds (Plate 9).

Repetition: 10 times

Duration: 5 minutes

Frequency: 3 set of 10 repetitions

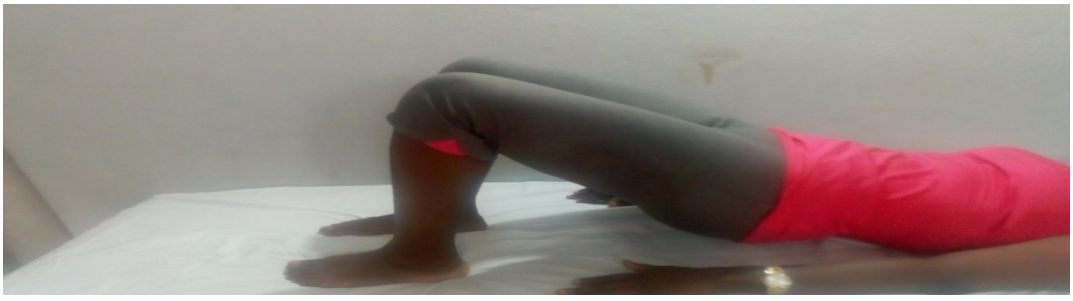

Plate 7. Isometric bridging exercises

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Plate 8. Isometric holding of the quadriceps

Sessions: Twice per week

(viii) Semi-squat in closed-chained position with both knees

Indication: Activation of the deep back muscles in functional position

Position: Semi-squat with both hands holding on the gymnasium hanger

Procedure: The researcher instructed the patient to go into semi-squat position such that the hip and knees were flexed while incorporating abdominal hollowing holding for 10 seconds (Plate 10).

Repetition: 10 times

Duration: 5 minutes

Frequency: 3 set of 10 repetitions

Sessions: Twice per week

(ix) Retraining proprioception with visual cue

Indication: Activation of the deep back muscles with Proprioception

Position: Sitting on a medicine ball with both knees bent to 90°, both hands in akimbo and eyes open.

Procedure: The researcher instructed the patient to sit on the medicine ball with both knees bent to 90° while

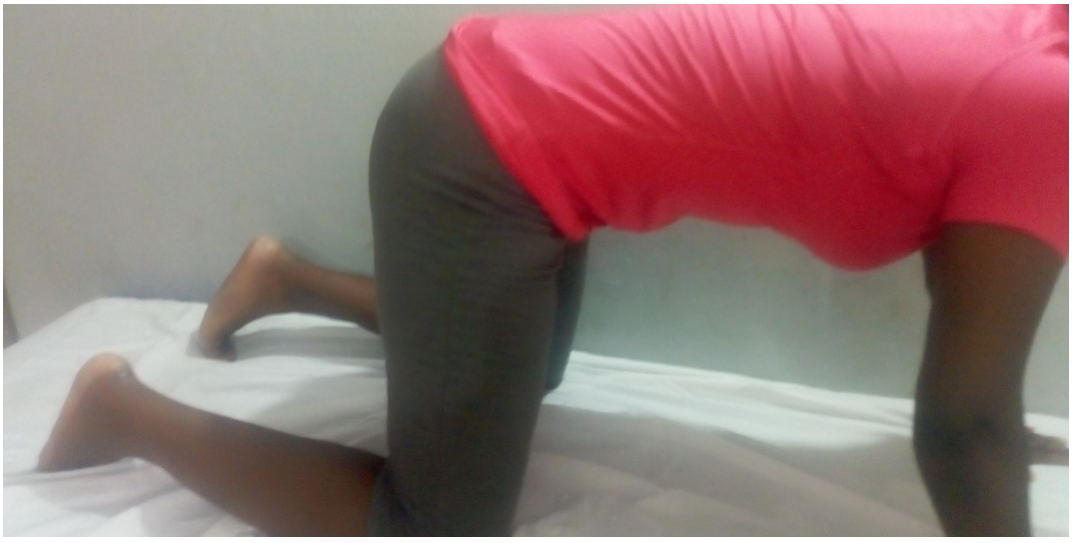

Plate 9. Stabilization in quadruple position

Plate 10. Semi-squat in close-chained position with both knees

incorporating abdominal hollowing holding for 10 seconds (Plate 11).

Repetition: 10 times

Duration: 5 minutes

Frequency: 3 set of 10 repetition

Sessions: Twice per week

(ix) Retraining proprioception without visual cue

Indication: Activation of the deep back muscles with Proprioception in absence of visual cue

Position: Sitting on a medicine ball with both knees bent to 90°, both hands in akimbo and eyes closed.

Procedure: The researcher instructed the patient to sit on the medicine ball with both knees bent to 90° while incorporating abdominal hollowing holding for 10 seconds (Plate 12).

Plate 12. Retraining proprioception without visual cue

Plate 11. Retraining proprioception with visual cue

Repetition: 10 times

Duration: 5 minutes

Frequency: 3 set of 10 repetition

Sessions: Twice per week

Phase three: High intensity exercises with open-chain segmental control

Leg loading, with hip flexion, extension, abduction or adduction, in positions such as lying, side lying, sitting or standing, were used to increase the strength of the trunk muscles. For all positions of leg loading, patients were expected to perform the abdominal hallowing.

(i) Leg loading with hip flexion

Indication: To strengthen the quadricep femoris

Position: Crook lying

Procedure: With one leg on the couch, the researcher instructed the patient to lift the other leg up holding for 10 seconds (Plate 13). Thereafter, repeat for the other leg.

Repetition: 15 times for each leg

Duration: 12 minutes

Frequency: 3 set of 15 repetitions each

Sessions: Twice per week

(ii) Leg loading in side lying

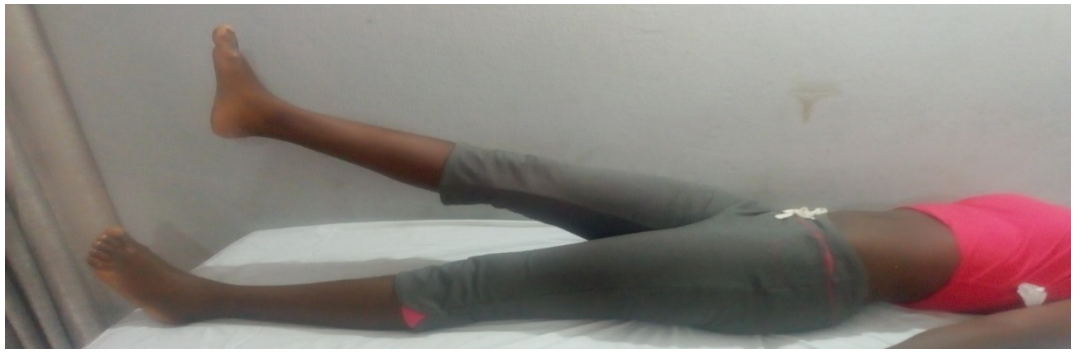

Plate 13. Leg loading with hip flexion

Indication: To strengthen the gluteus medius and minimus

Position: Side lying

Procedure: The researcher instructed the patient to lift the leg on top as high as possible holding for 10 seconds (Plate 14). Thereafter, repeat for the other leg.

Repetition: 15 times for each leg

Duration: 12 minutes

Frequency: 3 set of 10 repetitions each

Sessions: Twice per week

(iii) Alternate arm and leg raise in prone lying

Indication: To strengthen Gluteus Maximus and also to relax the hyperactive global back muscles.

Position: Prone lying

Procedure: The researcher instructed the patient to lift one arm and the opposite leg and hold both for 10 seconds (Plate 15). Thereafter, repeat for the alternate arm and leg.

Repetition: 15 times for each alternate arm and leg

Duration: 12 minutes

Frequency: 3 set of 15 repetitions each

Sessions: Twice per week

(iv) Leg loading of adductor magnus and brevis in open-chained position

Indication: To strengthen adductor magnus and brevis

Position: Side lying

Procedure: With one lower extremity fully crossed on the other in side lying, the researcher instructed the patient to lift the crossed leg up holding for 10 seconds (Plate 16). Thereafter, repeat for the other leg.

Repetition: 15 times for each leg

Duration: 12 minutes

Frequency: 3 set of 15 repetitions each

Sessions: Twice per week.

(v) Isometric holding of the iliopsoas in open-chained position

Indication: To strengthen the iliopsoas

Position: High sitting on the couch

Plate 14. Leg loading in side lying

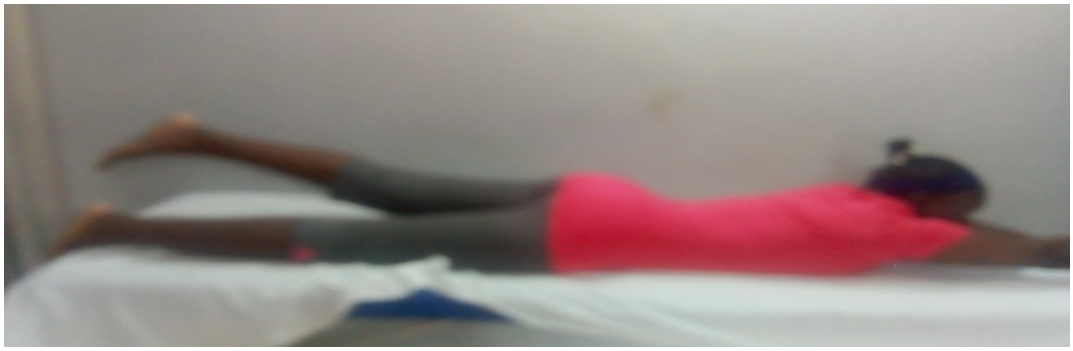

Plate 15. Alternate arm and leg raise in prone lying

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Procedure: The researcher instructed the patient to lift the thigh of one lower extremity with the other thigh on the couch, hold for 10 seconds (Plate 17). Thereafter, repeat for the other lower extremity.

Repetition: 15 times for each leg

Duration: 12 minutes

Frequency: 3 set of 15 repetitions

Sessions: Twice per week

(vi) Alternate arm and leg raise in quadruple position

Indication: To strengthen gluteus maximus and also to relax the hyperactive global back muscles.

Position: Both knees and hands on the couch (on all fours)

Procedure: The researcher instructed the patient to lift one arm and the opposite leg and hold both for 10 seconds (Plate 18). Thereafter, repeat for the alternate arm and leg.

Repetition: 15 times for each alternate arm and leg

Duration: 12 minutes

Frequency: 3 set of 15 repetitions each

Sessions: Twice per week

(vii) Semi-squat in open-chained position with both knees

Indication: Activation of the deep back muscles in functional position

Position: Semi-squat with outstretched upper extremity

Procedure: The researcher instructed the patient to go into semi-squat position such that the hip and knees were flexed and both upper extremities stretched out in the air while incorporating abdominal hollowing holding for 10 seconds (Plate 19).

Repetition: 15 times

Duration: 6 minutes

Frequency: 3 set of 15 repetition

Sessions: Twice per week

(vii) Semi-squat in open-chained position with one knee

Plate 16. Leg loading of adductor magnus and brevis in open-chained position

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Plate 17. Isometric holding of the Iliopsoas in open-chained position

Indication: Activation of the deep back muscles in functional position

Position: Semi-squat with outstretched upper extremity

Procedure: The researcher instructed the patient to go into semi-squat position with the knee of one lower extremity flexed, the hip of the other lower extremity flexed and both upper extremities stretched out in the air while incorporating abdominal hollowing holding for 10 seconds (Plate 20).

Repetition: 15 times

Duration: 6 minutes

Frequency: 3 set of 15 repetitions each

Sessions: Twice per week

(viii) Retraining proprioception in open-chained position with visual cue

Indication: Activation of the deep back muscles with Proprioception

Position: Sitting on a medicine ball with both knees bent to 90°, both hands stretched out in the air and eyes opened.

Procedure: The researcher instructed the patient to sit on the medicine ball with both knees bent to 90° while incorporating abdominal hollowing holding for 10 seconds (Plate 21).

Repetition: 15 times

Duration: 6 minutes

Frequency: 3 set of 15 repetition

Sessions: Twice per week

Plate 18. Alternate arm and leg raise in quadruple position

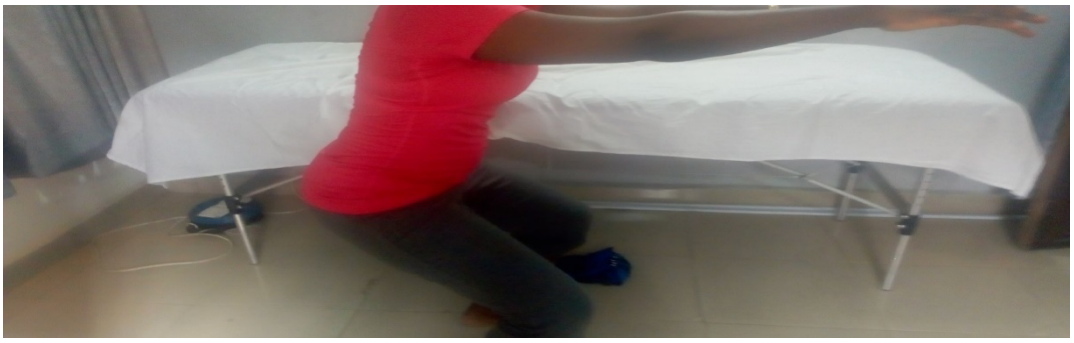

Plate 19. Semi-squat in open-chained position with both knees

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Plate 20. Semi-squat in open-chained position with one knee

(viii) Retraining proprioception in open-chained position without visual cue

Indication: Activation of the deep back muscles with proprioception

Position: Sitting on a medicine ball with both knees bent to 90°, both hands stretched out in the air and eyes closed.

Procedure: The researcher instructed the patient to sit on the medicine ball with both knees bent to 90° while incorporating abdominal hollowing holding for 10 seconds (Plate 22).

Repetition: 15 times

Duration: 6 minutes

Frequency: 3 set of 15 repetition

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Plate 22. Retraining proprioception in open-chained position without visual cue

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Plate 21. Retraining proprioception in open-chained position with visual cue

Sessions: Twice per week.

B. Graded activity exercise program

Exercise prescription

The GAE was conducted for 10 weeks of 20 exercise sessions in three phases. Exercise for individual participants lasted a minimum of 45 minutes for a session. The same types of exercises were used in the three phases of GAE intervention for patients with NSCLBP. Phase 1 consisted of only one session of GAE intervention, phase 2 comprised 9 sessions of GAE in five weeks, and phase 3 consisted of 10 sessions of GAE in five weeks.

The GAE comprises progressive strength and endurance exercises. An individually-based scheme was adopted on a time-contingent basis. Activities and exercises were gradually increased toward the pre-set goal,

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Plate 23. Quadriceps strengthening exercises

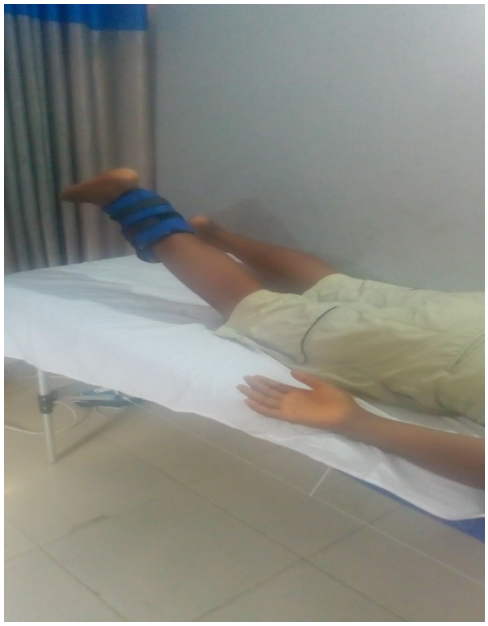

Plate 24. Hamstring strengthening exercises

starting slightly under baseline values. Patients were not allowed to under-perform nor over-perform their exercises, but they were encouraged to gradually tolerate their exercise programs as prescribed.

Exercise progression

As the patients' progressed with the exercise plan, the exercise dosage was increased to facilitate improvements in muscular strength and endurance using time contingency-management principles. Time-contingency-management means that graded exercises or activities are preset to quotas (i.e. the patients do not stop the exercises because of pain or other tolerance factors). Quotas (for endurance time or repetitions) were systematically increased to enable the patient to reach the goal of the strength and endurance training. The quotas were followed exactly, neither over-performed nor under-performed.

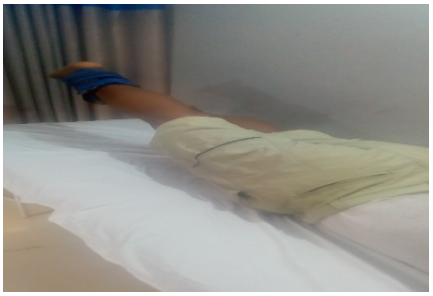

Plate 25. Gluteus maximus strengthening exercises

Thus, there was a shift from pain-contingency management during baseline measurements to time-contingency (quotas) management in the treatment phase. This was achieved by increasing the load (or intensity) from 1 kg to 3 kg, increasing the repetition per set, increasing the number of sets per exercise, decreasing the rest period between sets or exercises. An initial increase in the number of repetitions was recommended before an increase in load. When the participant can comfortably achieve the "upper limit" of the prescribed repetition range, for example, 10 or 15 repetitions, training loads are increased by 1, so that no more than expected repetitions are completed without volitional fatigue.

During the treatment phases, the researcher gave positive reinforcement of healthy or active behavior for successful completion of the quotas. To enhance patient motivation, pain behavior was extinguished. The increase in activities started at a lower level.

Exercise prescription for the phases of graded activity exercise intervention

Phase 1: One day (1 session) of GAE intervention

Repetition: 10 repetitions for each exercise

Duration: 45 minutes

Frequency: 1-3 set of 10 repetition

Plate 26. Back extension exercise

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Plate 27. Gluteus medius and minimus strengthening exercises

Sessions: Twice per week

Phase 2: 5 weeks (9 sessions) of GAE intervention

Repetition: 10 repetitions for each exercise

Duration: 45 minutes for a session

Frequency: 1-3 set of 10 repetition for each exercise

Sessions: Twice per week

Phase 3: 5 weeks (10 sessions) of GAE intervention

Repetition: 15-20 repetitions for each exercise

Duration exercise: 60 minutes per session

Frequency: 1-3 set of 10 repetition for each exercise

Sessions: Twice per week

(B) Prescribed graded activity exercise

(1) Quadriceps strengthening exercises

Patient position: High sitting with both knees flexed to 90°.

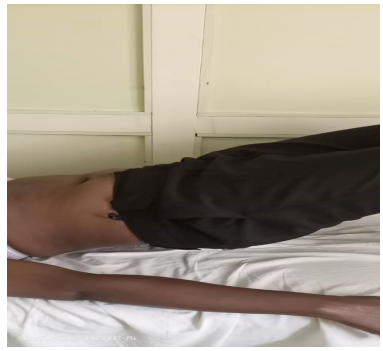

Plate 28. Bridging exercises Iranian Rehabilitation Journal

Procedure: The researcher anchors a 2 kg weight to the ankle of one lower extremity of the patient then instructed the patient to extend the knee and hold for 10 seconds (Plate 23). Thereafter, patient is instructed to repeat for the other lower extremity.

(2) Hamstring strengthening exercises

Patient position: Prone lying

Procedure: The researcher anchored 2kg weight resistance around one of the patients' ankles and instructed them to bend the knee to midway (45°) and hold for 10 seconds (Plate 24). Thereafter, repeat for the other leg.

(3) Gluteus maximus strengthening exercises

Patient position: Prone lying

Procedure: The researcher anchored 2 kg weight resistance around one of the patients' ankles and instructed them to lift the lower extremity with weight and hold for 10 seconds (Plate 25). Thereafter, repeat for the other leg.

(4) Back extension exercise

Patient position: Prone lying with both upper limbs by the sides.

Plate 29. Half bridging exercises Iranian Rehabilitation Journal

Plate 30. Curl up exercise

Procedure: The patient was instructed to lift up the head and upper back and hold for 10 seconds (Plate 26).

(5) Gluteus medius and minimus strengthening exercises

Patient position: Supine with both knees flexed to 90°.

Procedure: The researcher anchored resistance bands (thera-band) around the patients' knees and instructed them to abduct the hips (Plate 27).

(6) Bridging exercises

Patient position: Supine with both knees flexed and upper extremity by the sides

Procedure: The patient was instructed to lift up the buttocks and hold for 10 seconds (Plate 28).

(7) Half bridging exercises

Patient position: Supine with one knee flexed to 90° with 2 Kg weight wrapped around the ankle of the unflexed lower limb.

Procedure: The patient was instructed to lift up the buttocks with the unflexed knee and hold for 10 seconds (Plate 29). Thereafter, repeat with the other lower extremity.

(8) Curl up exercise

Patient Position: Supine with both knees flexed to 90°

Procedure: The patient was instructed to lift up the head with the upper trunk and touch the knees with both fingers then hold for 10 seconds (Plate 30).

(9) Bicycle ergometry

Warm-up: 2.5-minute with speed of 5–8 km/h;

Training intensity: 5-minutes of 4-unit resistant training and 5-minutes of 8-unit resistant training with 70-80% maximum heart rate calculated as: Maximum heart=220-age of patients (Plate 31).

Cool down: 2.5-minute slow-down with gradual speed reduction.

Plate 31. Bicycle ergometry

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