# **ORIGINAL ARTICLE**

# Analysis on the Combined Effect of Myofascial Release and Postero- Anterior Mobilisation in Chronic Non-Specific Low Back Pain

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#### ABSTRACT

Lumbar stiffness is a very common condition. About 60%-80% of population suffer from this condition at any stage of life. The incidence of low back pain has ranged between 4 to 14% in one year. There are many causes of lumbar stiffness like poor sitting posture, tight hamstring, facet joint osteoarthritis, etc. MFR is a group of specific movements that are directed towards the soft tissue particularly the muscle and fascia and used to treat myofascial pain syndrome, to restore the optimal length of fascial tissue, decrease pain and improve functionality. Mobilisation is a passive movement of a skeletal joint and used to restore the motion, relieve pain, and to treat joint dysfunction. To compare the immediate effect of MFR and PA mobilisation on ROM and function in patients with lumbar stiffness. Experimental Study design with 60 subjects based on the inclusion and exclusion criteria were recruited for the study. After obtaining informed consents, the patients were assigned into 2 groups; twenty of each. In group A conventional therapy and group B MFR with PA mobilisation were used. Pain was measured by VAS and lumbar flexion ROM was measured by modified Schober's test and functional ability was measured by Oswestry low back pain disability questionnaire. Both the groups showed a significant improvement in VAS, lumbar flexion ROM and ODI score with p value<0.001 after the treatment. This study can be concluded that MFR with the PA mobilization reduces pain and improves lumbar flexion ROM and functions in chronic non- specific low back pain.

Keywords - MFR, PA mobilisation, ROM, ODI, VAS.

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### INTRODUCTION

Lumbar spine is commonly known as low back. Lumbar stiffness or low back stiffness is a very common condition. About 60%-80% of population suffer from this condition at any stage of life [1]. The incidence of low back pain has ranged between 4% to 14% in one year [2]. Low back pain is the most common cause of activity limitation in young age people. Back pain is a broad topic with many potential etiologies that are broken mainly in four primary categories - Mechanical, degenerative, inflammatory, oncologic and infectious.

The annual prevalence of chronic low back pain has been reported from 15% to 45%, with a point prevalence of 30% [3]. Chronic low back pain have estimated that the average age-related prevalence of persistent low back pain is approximately 15% in adults and 27% in the elderly (18–21) [4]. Back pain is very common in the adult population. Some studies have shown that up to 23% of the world's adults suffer from chronic low back pain. This population has also shown a one-year recurrence rate of 24% to 80%. Some estimates of the lifetime prevalence are as high as 84% in the adult population. The prevalence is much less apparent in the pediatric literature. One Scandinavian study demonstrated that the point prevalence of back pain was approximately 1% for 12-year olds and 5% for 15-year-olds, with a cumulative incidence of 50% by age 18 for females and age 20 for males. An extensive systematic review demonstrated an annual rate of adolescents suffering from back pain of 11.8% to 33%.

Subjects with LBP are compliant to have decrease in spinal mobility and changes in the loading pattern of spine. Back stiffness is commonly caused by muscle spasm or lumbar arthritis. To differentiate the cause

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of lumbar spine stiffness depends upon the onset of symptoms. There are many causes of lumbar stiffness; tight hamstring, poor sitting posture, facet joint osteoarthritis [5]. Passive stiffness of the lumbar spine may be due to prolonged sitting, consequently, performing lumbar flexion movements after long period of sitting may increase the risk of low back injury [5]. Low back stiffness can be treated by various manual therapy techniques, it includes passive stretching, soft tissue mobilisation, myofascial release, manual traction, muscle energy technique, joint mobilisation and manipulation [6].

Myofascial release is a type of manual therapy technique that treats immobility and pain in skeletal muscles by improving blood and lymphatic circulation, by relaxing the contracted muscles and stimulating the stretch reflex in muscles [7]. Myofascial release technique described as "designed to stretch and reflex release patterned soft tissue and joint-related restrictions" [8]. MFR generally involves slow, sustained pressure applied to restricted fascial layers either directly (direct MFR technique) or indirectly (indirect MFR technique). Direct MFR technique is thought to work directly over the restricted fascia: practitioners use knuckles or elbow or other tools to slowly sink into the fascia, and the pressure of force applied is a few kilograms to contact the restricted fascia, apply tension, or stretch the fascia. Indirect MFR applies until the free movement is achieved. It involves a gentle stretch guided along the path of least resistance. The pressure applied is a few grams of force, and the hands moves towards the direction of fascial restrictions, the stretch will be hold for few seconds, and allow the fascia to loosen itself [9–12].

MFR is used in combined with conventional treatment is to be effective to provide immediate relief of pain and tissue tenderness. It has been hypothesized that fascial restrictions in one part of the body cause undue tension in other parts of the body, due to fascial continuity [2]; MFR is one of the most frequently applied and studied osteopathic manipulative treatment technique [13]. MFR is a group of specific movements that are directed towards the soft tissue of the body particularly the muscle and fascia. This technique is used to treat myofascial pain syndrome [8], to restore the optimal length of fascial tissue, decrease pain and improve functionality and release restriction [9,14,15].

Mobilisation is a slow, repetitive, rhythmical, oscillatory arthrokinematic and osteokinematic manual therapy movement. It is a passive movement of a skeletal joint used to restore the motion, relieve pain, and to treat joint dysfunctions [16]. Grades of the mobilisation is given by Maitland. Mobilisation may affect pain through a number of possible mechanism, because mobilisation directly deliver an external force to soft tissues and joints of the body [17]. Mobilisation are used in different dosages and various parameters form the basis of the treatment dosages, these includes force, amplitude, rate, repetition, and time [18,19]. PA mobilisation is frequently used by physiotherapists in the assessment of back pain and stiffness and involves the therapist applying a PA force over the spinous process of the patient in the prone position [20]. Postero-anterior mobilisation applied on the L3, L4 and L5 for three minutes produces increase in the lumbar mobility.

This study intends to analyse the combined effect of myofascial release and postero-anterior mobilisation in chronic non-specific low back pain.

#### MATERIAL AND METHODS

This experimental study involved 60 subjects both male and female between the age group 25 - 50 years, who were selected on convenient manner after fulling the diagnostic criteria for non-specific low back pain with Grade 2, 3,4 while suffering for at least 12 weeks [21].

Subjects with Spondylolisthesis, Spondylosis, Previous back surgery like – Laminectomy, Vertebroplasty, Discetomy, Fracture of lumbar spinal vertebra, Dislocation or structural defect of vertebral structure of lumbar region, Infectious disease of spine like- vertebral osteomyelitis, spinal epidural abscess, tuberculosis of spine etc. were completely excluded apart from the diagnostic criteria [14].

The study was conducted in the outpatient department for a period of 6 months. The effect of MFR and PA mobilisation on pain, lumbar ROM and diability were analysed using Visual analogue Scale [22], Lumbar flexion ROM- Modified Schober's test [23], Oswestry low back pain and disability questionnaire [24–26]. **Procedure** 

Post approval from ECM; before initiating the study, the procedure, possible risk and benefits were explained to the subjects and a signed consent was taken from the subjects. The 60 subjects were divided into two groups i.e. 30 subjects in each group. Group A – conventional therapy & Group B – MFR + mobilisation + conventional therapy. Subjects were assessed just prior and after the treatment procedure. **Group A (Control Group)** 

# IFT and moist heat were given to the patient. IFT involved placement of 4-pole electrode over lumbar area which will be stimulated for 10 minutes at a modulated frequency of 200Hz. Followed by Moist heat for 10 minutes. Patients were encouraged to perform;

- flexor regime exercise Pelvic Tilt, Knee to chest single and bilateral, Partial sit up.
- Pelvic Tilt Subject will lie on back with knees bent, feet flat on floor. Flatten the back against the floor, without pushing down with the legs. Hold for 5-10 seconds and 10 repetitions will be done.
- Single Knee to chest Subject will lie on back with knees bent and feet flat on the floor. Slowly pull right knee toward shoulder and hold for 5-10 seconds. Lower the knee and repeat with other leg. 10 repetitions will be done.
- Double knee to chest Begin as in the previous exercise. After pulling right knee to chest, pull left knee to chest and hold both knees for 5-10 seconds. Slowly lower one leg at a time. 10 repetitions will be done.
- Partial sit-up Patient will do pelvic tilt and while holding this position, slowly curl head and shoulders off the floor. Hold for 5-10 seconds. 10 repetitions will be done.

Control treatment will be given 3 days in a week for 4 weeks.

# Group B (Experimental Group)

Subjects were positioned in prone lying position & assessed to evaluate the hypomobile level of lumbar spine and PA mobilization will be perform at that level of lumbar spine. 3 cycles of large amplitude oscillatory PA glide with grade 3 mobilization according to Maitland and Edwards were given each cycle will be about 60 seconds. MFR was performed on back functional line, lattissimus dorsi, thoracolumbar fascia, and contralateral gluteal maximus and vastus lateralis muscles. The therapist works directly on restricted fascia by using knuckles or elbow to slowly sink into the fascia following which tension or stretch will be applied on fascia. The stretch will be hold and allow the fascia to loosen it.

Same conventional therapy will be given to the subjects, as carried out for the group A. Treatment was given 3 days in a week for 4 weeks.

## **Statistical Analysis**

Descriptive statistics was performed to find out mean, standard deviation for the demographic variable and outcome variables. Paired t-test was used to find out significant difference within group A and group B for VAS, lumbar ROM and Oswestry score. One way ANOVA test was used to find out significant difference between group A and group B for VAS, lumbar ROM and Oswestry score. Table 1 Frequency of Age in Group A

| Age Group | Frequency | Percent | <b>Cumulative Percent</b> |  |  |  |
|-----------|-----------|---------|---------------------------|--|--|--|
| 25-30     | 12        | 40      | 40                        |  |  |  |
| 31-35     | 8         | 26.7    | 66.7                      |  |  |  |
| 36-40     | 5         | 16.7    | 83.4                      |  |  |  |
| 41-45     | 5         | 16.7    | 100.1                     |  |  |  |
| Total     | 30        | 100.1   |                           |  |  |  |

**Table 2.** Frequency of Age in Group B

| Age Group | Frequency | Percent | Cumulative Percent |
|-----------|-----------|---------|--------------------|
| 25-30     | 11        | 36.7    | 36.7               |
| 31-35     | 8         | 26.7    | 63.4               |
| 35-40     | 11        | 36.7    | 100.1              |
| Total     | 30        | 100.1   |                    |

Table 1 and 2 shows the data of frequency for the age distribution with the cumulative percentage.

| Table 3: Baseline data for age |       |    |                |                 |  |  |
|--------------------------------|-------|----|----------------|-----------------|--|--|
| Age                            | Mean  | N  | Std. Deviation | Std. Error Mean |  |  |
| Group -A                       | 33.2  | 30 | 6.277          | 1.146           |  |  |
| Group -B                       | 33.23 | 30 | 4.644          | 0.848           |  |  |

Table 3 data shows 60 participants both male and female divided into two groups, 30 participants were included in Group A and 30 participants were included in Group B; where in the Group A the mean age is 33.20 and standard deviation (sd) is 6.277 with standard error mean of 1.146. In the Group B the mean age is 33.23 and sd is 4.644 with the standard error mean of 0.848.

| Paired Samples Test |  |                    |           |               |  |        |         |    |          |
|---------------------|--|--------------------|-----------|---------------|--|--------|---------|----|----------|
|                     |  | Paired Differences |           |               |  |        |         |    |          |
|                     |  |                    | Std.      | Std.<br>Error | 95% Confidence Interval<br>of the Difference |        |         |    | Sig. (2- |
|                     |  | Mean               | Deviation | Mean          | Lower  | Upper  | Т       | Df | tailed)  |
| Pair 1<br>Group A   | Pre VAS - Post VAS   | 1.567              | .568      | .104          | 1.354  | 1.779  | 15.099  | 29 | .000     |
| Pair 2<br>Group A   | Pre Lumbar flexion<br>ROM(cm) - Post Lumbar<br>Flexion ROM(cm) | -1.067             | .450      | .082          | -1.235                                       | 899    | -12.990 | 29 | .000     |
| Pair 3<br>Group A   | Pre Oswestry Score - Post<br>Oswestry Score                    | 4.167              | 1.877     | .343          | 3.466  | 4.868  | 12.159  | 29 | .000     |
| Pair 4<br>Group B   | Pre VAS - Post VAS   | 2.200              | .610      | .111          | 1.972  | 2.428  | 19.746  | 29 | .000     |
| Pair 5<br>Group B   | Pre Lumbar flexion<br>ROM(cm) - Post Lumbar<br>Flexion ROM(cm) | -1.467             | .819      | .150          | -1.773                                       | -1.161 | -9.805  | 29 | .000     |
| Pair 6<br>Group B   | Pre Oswestry Score - Post<br>Oswestry Score                    | 7.233              | 2.609     | .476          | 6.259  | 8.207  | 15.187  | 29 | .000     |

 Table 4. Pre- post VAS, lumbar flexion ROM and Oswestry score within Group A and Group B

In the Group A the mean of paired difference of the pre- post VAS was 1.567 with the standard deviation of .568 which was statistically significant (p value<.000). The pre-test scores are greater than post scores that is why the mean of paired difference was positive, this shows that VAS scores reduced significantly which indicates significant improvement in the pain of the participants. In the Group B the mean of paired difference of the pre- post VAS was 2.200 with the standard deviation of .610 which was statistically significant (p value<.000). The pre-test scores are greater than post scores which why the mean of paired difference is positive. This shows that VAS scores reduced significant improvement in the pain of the participants.

The mean of paired difference for VAS of Group B is greater than Group A it indicates that the Group B shows more improvement for VAS than the Group A.

In the Group A the mean of paired difference of the pre- post lumbar flexion ROM was -1.067 with the standard deviation of .450 which was statistically significant (p value<.000). The pre-test scores are lesser than post scores that is why the mean of paired difference was negative, this shows that lumbar ROM values increased significantly which indicants improvement in lumbar ROM of the participants. In the Group B the mean of paired difference of the pre- post lumbar flexion ROM was -1.467 with the standard deviation of .819 which was statistically significant (p value<.000). The pre-test scores are lesser than post scores that is why the mean of paired difference was negative, this shows that lumbar ROM values increased significantly which indicants improvement in lumbar ROM of the participants.

The mean of paired difference for lumbar ROM of Group B is lesser than Group A it indicates that the Group B shows more improvement in lumbar ROM than the Group A.

In the Group A the mean of paired difference of the pre- post Oswestry scores was 4.167 with the standard deviation of 1.877 which was statistically significant (p value<.000). The pre-test scores are greater than post test scores that is why the mean of paired difference was positive, this shows that Oswestry scores reduced significantly which indicates significant improvement in functions of the participants. In the Group B the mean of paired difference of the pre- post Oswestry score was 7.233 with the standard deviation of 2.609 which was statistically significant (p value<.000). The pre-test scores are greater than post scores that is why the mean of paired difference was positive, this shows that Oswestry scores reduced significantly which indicates significant improvement in functions of the participants.

The mean of paired difference for Oswestry score of Group B is greater than Group A it indicates that the Group B shows more improvement for Oswestry score than the group A.

# RESULTS

The outcome measure for pain shows the significant reduction in the VAS score for both group A and group B. But the mean of paired difference for VAS of Group B is greater than Group A it indicates that the Group B shows more improvement for VAS than the Group A.

The outcome measures for lumbar flexion ROM shows the significant improvement in the modified Schober's test scores for both group A and group B. but the mean of paired difference for lumbar ROM of

Group B is lesser than Group A it indicates that the Group B shows more improvement in lumbar ROM than the Group A.

The outcome measures for functional measurement shows the significant improvement in the Oswestry low back pain and disability questionnaire for both group A and group B. But the mean of paired difference for Oswestry score of Group B is greater than Group A it indicates that the Group B shows more improvement for Oswestry score than the group A.

When comparing both the groups, MFR with PA mobilization in group B shows the better improvement than conventional therapy in group A.

## DISCUSSION

Lumbar stiffness or low back pain is a very common condition. Low back pain is the most common cause of activity limitation in young age people. Subjects with LBP are compliant to have decrease in spinal mobility and changes in the loading pattern of spine. Back stiffness is commonly caused by muscle spasm or lumbar arthritis. To differentiate the cause of lumbar spine stiffness depends upon the onset of symptoms.

The aim of this research was to analyse the combined effect of myofascial release and postero anterior mobilization in chronic non-specific low back pain. Studies by Arguisuelas *et al*, in which patients received MFR on low back to reduce pain and disability for chronic low back pain [14]. The principal finding in this study is that the MFR intervention significantly effective in pain and disability in chronic low back patients. MFR has been reported to reduce pain and disability in chronic low back pain [2].

Literature shows that MFR is an effective technique in the improvement in the lumbar ROM in the patients with LBP. The findings of the study by Ellythy et al, are looking forward to see MFR as a part of manual techniques directed at the reducing pain and improving lumbar ROM in patients with chronic low back pain [8].

Studies of Shum et al, demonstrated significant improvement in reducing spinal stiffness, increasing spinal motion and reducing in magnitude and onset of pain [1]. These findings provide that PA mobilization is an effective technique in mobilizing the spine and relieving the symptoms of subjects with back pain. Furthermore study by Chesterton et al, (2017) concluded that L4 and L5 central PA mobilization have the ability to increase lumbar ROM. The findings of the study by Goodsell et al, indicate that PA mobilization is an effective technique to reduce in the intensity of pain in patients with low back pain [20].

According to the statistical analysis, the mean age of 60 participants (including male and female) where in the Group A the mean age is 33.20 and standard deviation (sd) is 6.277. In the Group B the mean age is 33.23 and sd is 4.644.

In the Group A the mean of paired difference of the pre- post VAS was 1.567 with the standard deviation of .568 which was statistically significant (p value<.000). In the Group B the mean of paired difference of the pre- post VAS was 2.200 with the standard deviation of .610 which was statistically significant (p value<.000). The pre-test scores are greater than post scores that is why the mean of paired difference was positive, this shows that VAS scores reduced significantly which indicates significant improvement in the pain of the participants.

In the Group A the mean of paired difference of the pre- post lumbar flexion ROM was -1.067 with the standard deviation of .450 which was statistically significant (p value<.000). In the Group B the mean of paired difference of the pre- post lumbar flexion ROM was -1.467 with the standard deviation of .819 which was statistically significant (p value<.000). The pre-test scores are lesser than post scores that is why the mean of paired difference was negative, this shows that lumbar ROM values increased significantly which indicants improvement in lumbar ROM of the participants.

In the Group A the mean of paired difference of the pre- post Oswestry scores was 4.167 with the standard deviation of 1.877 which was statistically significant (p value<.000). In the Group B the mean of paired difference of the pre- post Oswestry score was 7.233 with the standard deviation of 2.609 which was statistically significant (p value<.000). The pre-test scores are greater than post scores that is why the mean of paired difference was positive, this shows that Oswestry scores reduced significantly which indicates significant improvement in functions of the participants.

When comparing both groups the mean paired difference for VAS and Oswestry score are more in group B, and lumbar ROM score is less is group B than group A. it shows that group B has more improvement than the group A.

#### CONCLUSION

This study can be concluded that MFR with the PA mobilization reduces pain and improves lumbar flexion ROM and functions in chronic non- specific low back pain.

#### REFERENCES

- 1. Shum GL, Tsung BY, Lee RY. (2013). The immediate effect of posteroanterior mobilization on reducing back pain and the stiffness of the lumbar spine. Arch Phys Med Rehabil. 94(4):673-679.
- 2. Ajimsha MS, Daniel B, Chithra S. (2014). Effectiveness of Myofascial release in the management of chronic low back pain in nursing professionals. J Bodyw Mov Ther. 18(2):273-281.
- 3. Andersson GB. (1999). Epidemiological features of chronic low-back pain. The lancet. 354(9178):581-5. 4.
- 4. Manchikanti L, Singh V, Falco FJE, Benyamin RM, Hirsch JA. (2014). Epidemiology of low back pain in Adults. Neuromodulation. 17(S2):3-10.
- 5. Beach TAC, Parkinson RJ, Stothart JP, Callaghan JP. (2005). Effects of prolonged sitting on the passive flexion stiffness of the in vivo lumbar spine. Spine J. 5(2):145-154.
- 6. Wheeler AH, Hanley EN. (1995). Spine update nonoperative treatment for low back pain: Rest to restoration. Spine. 20(3):375-8.
- 7. Leboeuf-Yde C, Kyvik KO. (1998). At what age does low back pain become a common problem? A study of 29,424 individuals aged 12-41 years. Spine (Phila Pa 1976). 23(2):228-234.
- 8. Ellythy MA. (2011). Effectiveness of Myofascial Release Technique in Management of Patients with Chronic Low Back Pain. 16(7):151-157.
- 9. McLennan G. (2005). Research (SY). J Vasc Interv Radiol. 16(2):P3.
- 10. Adams MA. (2004). Biomechanics of back pain. Acupunct Med. 22(4):178-188.
- 11. Ajimsha MS. (2011). Effectiveness of direct vs indirect technique myofascial release in the management of tension-type headache. J Bodyw Mov Ther. 15(4):431-435.
- 12. Ajimsha MS, Al-Mudahka NR, Al-Madzhar JA. (2015). Effectiveness of myofascial release: Systematic review of randomized controlled trials. J Bodyw Mov Ther. 19(1):102-112.
- 13. Micheal A. Seffinger. (2014). OMT relieves low back pain The Somatic Connection. The Journal of the American Osteopathic Association. 114(1):61.
- 14. Arguisuelas MD, Lisón JF, Sánchez-Zuriaga D, Martínez-Hurtado I, Doménech-Fernández J. (2017). Effects of Myofascial Release in Non-specific Chronic Low Back Pain: A Randomized Clinical Trial. Spine (Phila Pa 1976). 42(9):627-634.
- 15. Arguisuelas Martinez MD, Lisón Párraga JF, Zuriaga DS, Martinez-Hurtado I, Fernández JD. (2018). Myofascial release improves pain and disability in non-specific chronic low back pain: A randomized clinical trial. J Bodyw Mov Ther. 22(4):857.
- 16. Kisner C, Colby LA. (2017). Therapeutic Exercise, Foundations and Techniques. Fa Davis.
- 17. Mior S, Smith B, Gribbin M. (2001). Manipulation and mobilization in the treatment of chronic pain. Clin J Pain. 17(4 SUPPL.).
- 18. Willett E, Hebron C, Krouwel O. (2010). The initial effects of different rates of lumbar mobilisations on pressure pain thresholds in asymptomatic subjects. Man Ther. 15(2):173-178.
- 19. Clark BC, Russ DW, Nakazawa M, et al. (2018). A randomized control trial to determine the effectiveness and physiological effects of spinal manipulation and spinal mobilization compared to each other and a sham condition in patients with chronic low back pain: Study protocol for The RELIEF Study. Contemp Clin Trials. 70(May):41-52.
- 20. Goodsell M, Lee M, Latimer J. (2000). Short-term effects of lumbar posteroanterior mobilization in individuals with low-back pain. J Manipulative Physiol Ther. 23(5):332-342.
- 21. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. (1992). Grading the severity of chronic pain. Pain. 50(2):133-149.
- 22. Boonstra AM, Schiphorst HR, Reneman MF, Posthumus JB, Stewart RE. (2008). Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain Int J Rehabil Res. 31:165-169.
- 23. Tousignant M, Poulin L, Marchand S, Viau A, Place C. (2005). The Modified-Modified Schober Test for range of motion assessment of lumbar flexion in patients with low back pain: A study of criterion validity, intra-and interrater reliability and minimum metrically detectable change. Disabil Rehabil. 27(10):553-559.
- 24. Brodke DS, Goz V, Lawrence BD, Spiker WR, Neese A, Hung M. (2017). Oswestry Disability Index: a psychometric analysis with 1,610 patients. Spine J. 17(3):321-327.
- 25. Davidson M, Keating JL. (2002). A Comparison of Five Low Back Disability Questionnaires. Phys Ther. 82(1):8-24.
- 26. Vianin M. (2008). Psychometric properties and clinical usefulness of the Oswestry Disability Index. J Chiropr Med. 7(4):161-163.

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