

Review Article

Review on the Effect of Mobilization-With-Movement and Eccentric Exercise in Lateral Epicondylitis

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Abstract

Background: Lateral epicondylitis is also acknowledged as tennis elbow is caused by injury to the proximal tendinous attachment of the extensor carpi radialis brevis. The condition is associated with people such as carpenters, musicians, sportspersons, housewives, typists, construction workers, etc. Manual physiotherapy techniques with established benefits in lateral epicondylitis are numerous.

Objective: To explore the effectiveness of Mobilization-with-Movement (MWM) and eccentric exercise on lateral epicondylitis (either in isolation or coupled with other treatment/s)

Study design: Narrative review

Method: Several electronic databases were searched from January 2019 to February 2020. The eligibility for inclusion was examined by two reviewers through the evaluation of the article abstract and full article. Methodological quality was assessed by employing PEDro scale. At least one functional/ disability outcome measures such as pain scale, isometric grip strength, pain-pressure threshold, and relevant questionnaires were used in the studies.

Results: 21 articles (9 for MWM and 12 for eccentric exercises) were included. Remarkably superior improvements were observed in all studies following MWM treatment whereas in the case of studies with eccentric exercise, although beneficial improvements were seen in all studies, only 7 out of 12 studies showed superior improvement as compared to other therapies.

Conclusions: Significant improvement in pain and movements in lateral epicondylitis with MWM. Eccentric exercise shown to be effective as adjunct in multimodal therapy. There is underpowered evidence of utilization of these approaches differentiating acute and chronic cases.

Keywords: Tennis elbow, physiotherapy, Mobilization with Movement, eccentric exercise.

Introduction

The lateral epicondylitis (LE) moreover also acknowledged as tennis elbow is caused by injury to the beaver muscle i.e. at the proximal tendinous attachment of ECRB (extensor carpi radialis brevis).

The extensor digitorum communis may likewise be injured and infrequently the extensor carpi radialis longus in a few cases, all in the level of proximal attachment of the extensors. The common symptom can be identified as discomfort and aching sensation at the lateral epicondyle. Furthermore, this pain is aggravated when the individual attempts wrist extension or supination. Along with pain and restriction of movement, the grip strength and sensitivity in those muscles are also affected.¹⁻⁵

Lateral epicondylitis, also known as “tennis elbow”, is documented in about 5-10% of sportspersons and also in people performing various tasks requiring excessive and repetitive effort involving gripping and supination-pronation

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movements such as carpenters, musicians, housewives, typists, construction workers, factory workers, etc. Every year, about 1-3% of the general population gets affected by this condition. Tennis players have a probability of 40-50% of being affected by lateral epicondylitis.⁶⁻⁸

There is an abundant debate for the exact pathology of lateral epicondylitis, and there still exists no agreement. Existing evidence following surgical intervention shows that it is a chronic disorder, and instead of inflammatory cells, there is the presence of degenerative changes like increased fibroblasts and disorganized collagen. These findings contradict the extensively used term epicondylitis which designates an inflammatory disorder. There has been a recent recommendation that the term epicondylitis is replaced with epicondylitis, which is a more precise descriptor of the underlying degenerative process.⁹⁻¹³

The degenerative process in this condition is said to originate due to repetitive microtrauma. A few examinations looking at the surgical examples and cadaveric examples demonstrate that this condition develops through a gradually developing phase, starting with degenerative angiogenesis and closures with fibrosis and calcification.¹⁴

This condition is encountered by approximately 2/5th of the common population sooner or later during their lifetime. The incidence is found in both men as well as in women aged 35 - 54 years. The documented prevalence is found to be around 4-7 for every 1000 patients going to therapeutic setup.¹⁵⁻²⁵

Among all the manual therapies used around the globe, MWM i.e. Mobilization-With-Movement is presently acquiring tremendous recognition. This technique of Mulligan is prescribed if; during its application it allows the painful joint to be moved freely without any pain or disablement. In MWM, the application of a glide or translation is performed in a perpendicular direction to the plane of the affected movement which is being performed during the glide. In the recent observations, mobilization-with-movement has been gaining a good reputation for treating various musculoskeletal disorders, many of which were found to be difficult to be treated by other treatment approaches and manipulation techniques (e.g. lateral epicondylitis, De Quervain's disorder).²⁶⁻²⁸

Eccentric contraction of an active muscle is the lengthening of the muscle under any load or weight. When eccentric contractions are performed multiple times for muscle training then it is termed as eccentric exercise/training. The primary objective of this exercise focuses on braking or slowing down the elongation process of a muscle which provides a challenge for the muscle, leading to increases in muscle strength, quicker healing, and improved metabolic rate. It delivers a braking mechanism for the muscle-tendon groups undergoing concentric movements to protect the joint/s from possible injury as the contraction is released.²⁹ Studies have proved an improvement in muscular properties, particularly viscoelasticity using an eccentric approach.³⁰ Sportspeople, elderly people, and patients desiring to retrain their muscles and tendons have found to obtain great benefit from eccentric exercises.³¹

Various treatment alternatives being proposed for the recovery of patients with lateral epicondylitis however, the practicability of those therapy procedures is generally doubtful and there is a necessity for further research. Recovery from lateral epicondylitis may incorporate exercise, deep-friction massage, manipulation, taping, acupuncture, orthotics, ultrasound therapy, modification of ADL and enough rest, or a break from work. For example, Kinesio-taping has also proved to be beneficial when used alone or together with physical therapy.³² Comparisons between treatment approaches like ultrasound, corticosteroids, and diathermy use exist.^{33,34} In a few chronic cases, arthroscopic procedures are also favoured.³⁵ Systematic reviews employed for specific approaches such as deep-friction massage³⁶ can be accessed from electronic databases. Distinguishing an effective treatment program for patients with lateral epicondylitis would have noteworthy advantages for quiet recuperation and will likewise include enhanced treatment benefits.³⁷⁻³⁹

There is the existence of an exceptional number of studies that suggest the deployment of mobilization -with-movement as a curative approach for clients visiting with lateral epicondylitis. Furthermore, for the same condition, a good quantity of studies have been performed on eccentric exercises as well. We intend to perform a narrative review of the formerly completed clinical trials to assess the efficacy of MWM and eccentric exercise in lateral epicondylitis by conducting an evidence-based study.

Method

The review was performed based on the quality recommendations for narrative review and study protocol provided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).⁴⁰

• Search strategy

A comprehensive search of a full set of the following electronic databases: (Pubmed, Medline, Scopus, Researchgate, Science Direct, Physiotherapy Evidence Database PEDro) was performed to recognize and select all studies from January 2019 up to February 2020 concerned with the implementation of MWM or eccentric exercise in lateral epicondylitis. The databases were independently searched by two researchers (RM and SH).

The keywords used for the search were: tennis elbow, physiotherapy, LE, lateral epicondylitis, lateral epicondylitis, RCT, mobilization with movement, eccentric exercise, manipulation, MWM. In this review, the word epicondylitis has been used interchangeably with epicondylitis for the ease of article search and the pooling of results. Search for other articles was made by going through the reference list of all included studies and picking up the articles which had been missed out during the initial selection.

Upon retrieval of articles from the above search strategy, screening of all titles and abstracts was done for identifying the studies that included the outcomes of mobilization-with-movement and/or eccentric exercise on lateral epicondylitis. To build up the qualification for the incorporation of these articles, their full texts were read and assessed. In case of insufficiency of any of the abstracts to reveal the suitability for the study, the full-text article was examined and the choice was made based on a consensual agreement between the authors.

• Study selection criteria

The studies considered eligible to be included in this review were randomized controlled design trials, controlled clinical design trials, or prospective randomized design trials. Along with this, the following criteria had to be fulfilled:

- ◇ Comparison between at least one treatment group and one control group; the treatment group would include at least one physical intervention involving either mobilization-with-movement or eccentric exercise, either solely or in combination with other interventions
- ◇ Participants with a diagnosis of tennis elbow or LE, confirmed by lateral elbow pain that

increased on palpation and/or during resisted wrist extension or using diagnostic tests by a general medical practitioner

- ◇ Incorporation of no less than one significant outcome measure, such as pain, muscle strength, and applicable questionnaires, etc

The English language was also an inseparable criterion for the fulfillment of necessities for inclusion.

Quality assessment

The PEDro scale was utilized to infer the methodological quality. Maher et al⁴¹ have confirmed its reliability of this 11 point scale for scoring the RCTs on the Physiotherapy Evidence Database. It has been broadly utilized as a part of recent surveys. It addresses the issues of eligibility criteria, randomization, allocation, blinding of the involved people, statistics, outcomes measures, and reporting of data. This scale helps to evaluate and estimate the validity of the research work.

Each of the 11 criteria was accompanied by a specific description and was scored either yes =1 point or no = 0 point. The maximum score is 11, a minimum of 6 out of 11 points (more than 50%) was decided as the benchmark for inclusion in the review. Studies were considered as a high-quality level if the score was 6 or more; as a fair quality level if the score was 4-5; and as poor quality level, if the score was 3 or less. The final decision regarding the PEDro score was made after a consensual agreement between the authors.

Data extraction and analysis

After screening and finalizing the articles to be included in the review, every article was read in full, a homogeneous set of data was assimilated independently by the two researchers (RM and SH). The information was segregated in subtopics regarding

- (i) authors along with the year of study.
- (ii) demographics of the patient sample.
- (iii) study design.
- (iv) intervention for the treatment group/s and control group/s.
- (v) the frequency of the treatment.
- (vi) outcome measures.
- (vii) outcomes and
- (viii) follow-up.

After obtaining the total from the PEDro scores; comparisons were made between the studies.

Results

After the initial search in August 2019, 197 articles were retrieved; later in February 2020, 3 more articles were added after a further search using other sources and databases. The figures as outlined depict the selection process after retrieval of the individual articles. The selected titles and/or the abstracts were subjected to preliminary screening, after which 103 articles were included and the rest were exempted for the reason that of duplication of data. The residual articles were re-assessed, 28 studies were irrelevant to lateral epicondylitis, 16 of the studies were done on a single subject and 13 studies did not have the usage of either eccentric exercise or MWM used.

Full-text article screening was done for the remaining 46 articles, out of which 5 articles were excluded as they had PEDro scores less than 50%, 7 articles were excluded as they involved experimentally induced lateral epicondylitis and 1 article was excluded as the intervention used in it wasn't related to physiotherapy.

The additional search which was carried out in February 2020 retrieved 3 more possible inclusions for the review.^{48, 49, 61} A final of 21 studies was selected for inclusion in the review, 12 of them being studies concerning eccentric exercises for lateral epicondylitis, and 9 studies concerning MWM for the same.

Among the selected 21 studies, the most repeatedly used outcome measure were Visual analogue scale for pain perception^{38,43,45,47-58,61} and PFGS for grip strength.^{38,42-45,47-49,51,54,56,58,60} Eleven studies implicated different functional questionnaires namely PRTEE, DASH, TEFS and SF-36 regarding the patient's function, pain and disability.^{45,46,48,49,51,54,55,56,59,60,61} Pain pressure threshold was assessed in two studies.^{42,44} Sympatho-excitatory and hypoalgesic assessment was done for a single study.⁴⁴

Risk of bias in included studies

After the assessment of the methodological quality of the studies using the PEDro scale, we were able to discover a few issues of potential biases. Seven out of twenty-one studies used concealed allocation of subjects.^{38,44,48,49,54,59,60} Baseline comparison wasn't performed in seven of the studies,^{42,46,47,48,49,55,59} the drop-out rate was more than 15% for two studies^{43,61} and intention-to-treat analysis wasn't stated in three of the eccentric studies.^{50,57,59} Blinding the patient or the therapist who performs the treatment might result in potential bias in the studies which are concerned with physiotherapeutic treatments. The treating

therapist wasn't blinded in any of the included studies, whereas in eight studies the patients were blinded to the treatments.^{38,42,44,46,49,54,56,58} Eight studies^{38,42,44,54,55,56,57,59} have used blinded assessors which also might result in producing biased results. For all the studies the criteria of between-group analysis of at least one outcome measure were fulfilled, and also point measures and variations of the listed outcome measures were reported.

Multiple studies incorporated some similar form of treatment to the control group as well^{43,46,48,53,54,56,60,61} which may cause synergistic effect bias in the results.

Effects of Mobilization-with-movement

As shown in Table 1 nine studies (n=480) were selected on behalf of MWM. The studies dated from 2001 to 2020.

Three studies investigated the efficacy of MWM (alone or with intervention) versus the "wait and see" group which meant that they were given information about the disease process and provided with practical advice on self-management and ergonomics.^{38, 42, 44}

Four of the studies didn't specify the follow-up in their articles. Hence these studies didn't provide any data on the effectiveness of the treatment during follow-up.^{5,39,42,43} The studies which investigated the efficacy of MWM against the placebo technique and the "wait and see" group found that the MWM group showed improvement of patient function and immediate reduction of pain after the session; there were minimal changes regarding PFGS in control and the placebo groups during and after treatment from baseline.^{38,42,44} The application of MWM was able to demonstrate hypoalgesic and concurrent beneficiary sympathoexcitatory effects similar to that of spinal manipulations, along with that the patients also gained improvement in pain threshold and grip strength.⁴⁴ The efficacy of MWM was also examined against corticosteroid injection by Bisset et al³⁸ the results showed that although initially, the injection showed better results but long term effects after 52 weeks showed greater statistical improvements in the MWM group, and the recurrence rate was drastically high as 72% in the injection group whereas it was found to be 8% in the MWM group.

The effects of MWM along with electrotherapy versus sham MWM along with electrotherapy showed significantly better outcomes for the MWM group in all the functional subscales of PRTEE.⁴⁶ In studies where taping was performed over the affected elbow after

the MWM session, the researchers found that patients were able to achieve improvement in grip strength and reduction in the pain intensity.^{45,47}

Martinez et al⁴⁸ performed a pilot study in 2017 which investigated the effects of MWM along with positive expectations given to the individual in written form versus MWM with negative expectations towards MWM. A wide range of outcome measures was utilized for this study out of which, the treatment group excelled significantly in the short version of the Tampa scale of Kinesiophobia, also the functional questionnaires – DASH and PRTEE showed improved perceived disability of better figures in the treatment group. A recent study performed by Reyhan et al (2019) showed favorable improvement on pain reduction, grip strength, and global improvement based on the PRTEE questionnaire when MWM was accompanied with cryotherapy and home exercises, they suggested future studies on a larger number of participants.⁴⁹

Effects of eccentric exercise

Twelve studies were included (n=705) representing eccentric exercises for lateral epicondylitis in Table 2 which dated from 2001 to 2018.

Five studies investigated the efficacy of eccentric exercises along with stretching as compared with other interventions.^{50,51,53,54} Svernlöv & Adolfsen⁵⁰ carried out the study with the long-term follow up of 12 months, they found long-lasting excellent recoveries in more than 95% of the subjects. Martinez et al⁵¹ conducted a similar study where the outcome measures used were pain, DASH questionnaire, PRFEQ, and grip strength; concentric exercises and stretching produced similar beneficial effects to the treatment group who received eccentric exercises along with stretching.

Cyriax techniques were also implicated for comparison in two studies.^{52,55} Among them, D Stasinopoulos implicated Cyriax technique, and Bioptron light against supervised eccentric exercises and stretching; pain reduction and improvement in grip strength were seen better ($p < 0.05$) in the group which received supervised eccentric exercises. Nagrle⁵⁵ compared the efficacy of eccentric exercises and phonophoresis versus a group administered with Cyriax physiotherapy and the outcome measures showed no difference at baseline; although both the groups gained significant improvements in the 4th and 8th weeks, the Cyriax group garnered better statistical improvements.⁵⁵

In 2011, a prospective randomized study was done to investigate the effects of eccentric strengthening for chronic lateral epicondylitis on 28 adults. The treatment group was administered eccentric strengthening exercises whereas the control group was administered iontophoresis, ultrasound, and stretching. The results depicted that after the completion of 4 weeks, both groups showed a decrease in pain scores, but no statistically significant differences were found in the two groups.⁵⁷

Multimodal treatment for lateral epicondylitis was performed by Croisier et al⁵⁴ and Tyler et al⁵⁶ by incorporating eccentric exercises along with deep friction massage, ultrasound, TENS, ice, stretching. Both studies resulted in the multimodal groups excelling statistically than the control groups in pain reduction (VAS) and improvement in functional scales (TEFS) after a follow-up period of 8-9 weeks.

Soderberg et al⁵⁸ performed a study on subjects suffering from chronic LE to assess temporary changes after administering eccentric exercise each day. The outcome measure used for the study was functional pain-free hand strength. The treatment group was administered eccentric training and a forearm band whereas the control group was administered warm-up exercises and a forearm band. Their results showed better results in the treatment group in terms of achieving the aim however, less significant differences were found for global perceived pain.⁵⁸

Thomas and Caroline⁵⁹ compared Astym treatment with the control group receiving eccentric exercise. The Astym group showed better improvement in outcome measures; DASH ($p < 0.05$) and Maximum Grip Strength ($p < 0.05$) after treatment for 4 weeks.⁵⁹ In one of the recent studies, eccentric exercise and therapeutic elastic taping were used as a treatment measure, compared with eccentric exercise along with sham taping. The results didn't show any statistically significant within-group differences in any outcome measures (PRTEE, SF-36, PFGS) after 0, 3, and 6 months in these groups; concluding that exercise alone and/or natural recovery may gradually improve the condition.⁶⁰ In one of the recent studies performed by J Nowotny,⁶¹ significant improvements were obtained when wrist orthosis was administered in unison with supervised eccentric exercises showing long-term benefits, compared with eccentric exercises alone.

Table 1 – Summary of MWM (Mobilization-with-movement) articles

Author/s and year of study	Sample size (male, female)	Study design	Intervention for the treatment group	Intervention for the control group/treatment group 2	Frequency	Outcome measures	Outcomes	Follow up									
Vicenzino <i>et al</i> (Year: 2001)	24 (14,10)	Randomized placebo-controlled repeated measures	Group 1: MWM Group 2: Placebo technique	General information about the condition and safety measures “wait and see”	3 sessions for each subject given on 3 different days, all more than 48 hours spaced out	PFGS, PPT	<table><tr><th>MWM</th><th>Placebo</th><th>Control group</th></tr><tr><td>58% improvement/progress was documented in PFGS</td><td>10.3% improvement/progress was documented in PFGS</td><td>5.5% reduction in grip strength was in PFGS</td></tr><tr><td>10.2% improvement/progress was documented in PPT</td><td>3.8% reduction was documented in PPT</td><td>0.3% improvement/progress was documented in PPT</td></tr></table> Using ANOVA, the MWM group produced statistically significant better outcomes as compared with the other two groups (p<0.0001)	MWM	Placebo	Control group	58% improvement/progress was documented in PFGS	10.3% improvement/progress was documented in PFGS	5.5% reduction in grip strength was in PFGS	10.2% improvement/progress was documented in PPT	3.8% reduction was documented in PPT	0.3% improvement/progress was documented in PPT	Outcomes taken throughout and post-treatment
MWM	Placebo	Control group															
58% improvement/progress was documented in PFGS	10.3% improvement/progress was documented in PFGS	5.5% reduction in grip strength was in PFGS															
10.2% improvement/progress was documented in PPT	3.8% reduction was documented in PPT	0.3% improvement/progress was documented in PPT															
Kochar and Dogra (Year: 2002)	66 (36,30)	Randomized controlled trial. Control group was- randomized	Group 1: MWM+ Ultrasound therapy + progressive exercise protocol Group 2: Ultrasound therapy + progressive exercise protocol	Progressive exercise protocol: Stretching; progressive resisted Isometric, Eccentric and concentric exercises	10 sessions for 3 weeks	Pain: VAS; grip strength; weight test	In Group 1 (MWM administered along with ultrasound and progressive exercises) statistically better outcomes were documented after week 12 as follows: VAS improvement which was greater than both the ultrasound group (p<0.05) and the control (p<0.05) Increase in strength was greater than the control (p<0.05) but not significantly better than Ultrasound group Improvement in weight test was superior than both the ultrasound group (p<0.01) and also the control (p<0.001)	1 st , 2 nd , 3 rd week then followed by progressive exercise routine designed for 12 weeks									
Paungmali <i>et al</i> (Year: 2003)	24 (17,7)	Randomized repeated measure study	1. MWM 2. Placebo technique	Control group : General information about the condition and safety measures “wait and see”	3 sessions for each subject given on 3 PFGS, and different days, a total gap of 48 hours or more between each session	Patient's grip strength using PFGS, Patient's pain using PPT and activity of SNS	The PFGS showed 47.5 percent increment in MWM group whereas negligible improvement was seen in other groups. The PPT was 281.4 kPa which reached 300.8 kPa in case of MWM group, it didn't change in the placebo group and decreased in the control group. Quantifiable increments were also observed for SNS function in MWM group. MWM group was found to produce favorable hypoalgesic effects and SNS activity similar to effects that of spinal manipulation.	Outcomes taken throughout and post-treatment									
Bisset <i>et al</i> (Year: 2006)	198 (128,70)	Randomized controlled trial	1. MWM and exercise 2. Injection with corticosteroids	General information about the condition and safety measures “wait and see”	MWM was given for 6 weeks, a total of 8 sessions	Pain: VAS; Grip strength, overall/in general percentage improvement	In the MWM group 65% success after therapy was found after 6 weeks, then 95% success after therapy was found after 52 weeks; showing better outcomes compared to other two groups at 52 weeks (Number needed to treat=4); The high recurrence rate of 72% was found patients who were given the injection as compared to 8% in MWM	6 th and 52 nd weeks									
Amro <i>et al</i> (Year: 2010)	34 (24,10)	Randomized controlled trial	MWM along with taping	Traditional routine therapy	3 sessions per week for 4 weeks	Pain: VAS, and PRTEE, MGS	Both the groups demonstrated significant improvement for all the outcome measure (p<0.05) VAS showed better improvement in MWM group than the control group:p<0.01 PRTEE also showed better improvement in MWM group : p<0.005 MGS measurement showed no significant dissimilar data	Not specified									

Laurentius <i>et al</i> (Year: 2012)	10	Randomized design placebo-controlled pilot survey	MWM along with US, hot pack, TENS, massage using deep friction	Sham MWM with US, hot pack, TENS, massage using deep friction	1 session/day for 10 days	PRTEE was used to assess pain and functional activities	After 10 days, the experimental group showed better improvement in all the aspects: Decrement in pain : (25.0% - 48.5%) as compared to control group (8.6% - 14.8%) Improvement in specific activity: (39.1% - 51.4%) as compared to control group (10.7% - 19.3%) For the usual activities: (42.8% - 51.2%) as compared to control group (3.8% - 12.5%)	Not specified
Sahar <i>et al</i> (Year: 2017)	60 (23,37)	Randomized controlled sign	MWM, this was followed by the US, stretching, TENS, taping, & eccentric exercises (n=30)	US, stretching, TENS, & eccentric exercises (n=30)	Per week 3 sessions for 4 weeks (12 sessions)	Pain: VAS, To calculate the digital dynamometer (hand-held) was utilized: PFGS	Both the groups demonstrated significant improvement for both outcome measures For pain using VAS: Pre-treatment: (6.07±0.64) and in post-treatment: (1.44±1.05) with p=0.001 in treatment group Pre-treatment (5.68±0.95) and in post-treatment: (4.52±0.97) with p=0.001 in control group PFGS readings in dynamometer : Pre-treatment: (12.65±3.72) and in post-treatment was: (20.93±5.24) with p=0.001 in the treatment group Pre-treatment: (11.71±2.31) and in post-treatment was: (13.67±2.92) with p=0.001 in control group Between group comparison using the MANOVA demonstrated better significant improvement in treatment group than the control group (p<0.05)	Not specified
Francisco <i>et al</i> (Year: 2017)	24 (11,13)	Pilot randomized controlled design trial	MWM was administered alongside positive expectations towards the therapy using written instructions	MWM was administered alongside negative expectations towards the therapy using written instructions	3 sessions for each subject on 3 different days, all more than 48 hours spaced out	PPDT, PFGS, At the baseline & via Mann-Whitney (p=0.015) No statistical differences found for other measures of outcome in the same group, using Wilcoxon test (Z=-2.27 ; r=-0.67 ; P=0.023) PRTEE in the group with positive expectations PRTEE: (Z=-2.934; r=0.47; P=0.003) findings at baseline and at end-of-treatment were compared No statistical differences found for other measures of outcome	PPDT improved better in the group with positive expectations VAS improved better in the treatment group after follow up at 1 st and 3 rd month via Mann-Whitney test (p=0.040) VAS (night-pain) improved in both the groups, no statistical differences were found between the groups Pain-free grip strength had statistically significant improvement better in treatment group (p<0.05) Similarly PRTEE scores also showed significantly better improvement in treatment group (p<0.05)	Not specified
Reyhan <i>et al</i> (Year: 2019)	40	Randomized controlled sign	MWM was administered along with cryotherapy and home exercises	Cryotherapy and home exercises	5 sessions/week for each subject for 2 weeks	VAS, VAS(night-pain) Pain-free Grip Strength and PRTEE	VAS improved better in the treatment group after follow up at 1 st and 3 rd month via Mann-Whitney test (p=0.040) VAS (night-pain) improved in both the groups, no statistical differences were found between the groups Pain-free grip strength had statistically significant improvement better in treatment group (p<0.05) Similarly PRTEE scores also showed significantly better improvement in treatment group (p<0.05)	1 st month and 3 rd month

SNS: Sympathetic Nervous System; MWM: Mobilization With Movement; PFGS: Pain-free Grip Strength; ANOVA: Analysis of Variance; VAS: Visual Analogue Scale; PRTEE: Patient Rated Tennis Elbow Evaluation; MGS: Maximum Grip Strength; US: Ultrasound; TENS: Transcutaneous Electrical Neuromuscular Stimulation; PPDT: Pressure-pain detection threshold; PPI: Perceived Pain Intensity; MANOVA: Multivariate Analysis of Variance; DASH: Disabilities of the Arm, Shoulder and Hand
*Statistical significance: p<0.05

Table 2 – Summary of eccentric exercise articles

Author/s and Year of study	Sample size (male, female)	Study design	Intervention for the treatment group	Intervention for control group/treatment group 2	Frequency	Outcome measures	Outcomes	Follow up
Svernlöv & Adolfsson (Year: 2001)	30 (19, 11)	Randomized pilot design study	Eccentric exercises followed by stretching (n=15)	Contract-relax stretch exercise (n=15)	12 weeks Each home session per day	Grip strength was assessed with strain-gauge. For pain: VAS was assessed at rest, then on palpation, and extension of the middle finger and resisted wrist extension on 3 rd , 6 th and 12 th month	<p>Treatment group</p> <p>For grip-strength: Taken at baseline month 0 = (from 28.6 to 71.8): 45.3 kg</p> <p>At 3rd month = (from 32.3 to 90.0): 53.1 kg</p> <p>At 6th month = (from 36.9 to 81.5): 54.2 kg</p> <p>At 12th month = (from 35.3 to 92.3): 66.0 kg</p> <p>The eccentric group showed better improvement in grip strength (p<0.05)</p> <p>None statistically significant dissimilar data were obtained for VAS</p>	3, 6 and 12 months
Martinez-Silvestrini <i>et al</i> (Year: 2005)	94 (50, 44)	Randomized controlled design trial	Eccentric exercises followed by stretching (n=27)	<p>For 1st Control group by C1: eccentric exercises followed by stretching (n=26)</p> <p>For 2nd control group Only Stretching (n=28)</p>	<p>Eccentric/centric exercise: Each day 3 sets were performed with 10 repetitions in each set; Rest: 5 minutes between every 2nd set</p> <p>Stretching: Each C2: day twice with 3 repetitions each (30 seconds stretch)</p> <p>Rest: 30 sec between each stretch</p>	<p>For pain: VAS, For grip strength: PFGS, DASH questionnaire, PRFEQ, SF-36 (Week 0, Week 6)</p>	<p>Data for pain:</p> <p>Taken at baseline C1 taken at baseline = 49 ± 21 SD</p> <p>At 6th wk = 24 ± 24 SD C1 taken at baseline wk 0 = 48 ± 21 SD</p> <p>Data for function – DASH C2 at 6th wk = 25 ± 24 SD</p> <p>Taken at baseline wk 0 Function – DASH</p> <p>C1 Taken at baseline wk 0 = 25 ± 13 SD</p> <p>At 6th wk = 16 ± 15 SD C1 wk 6 = 17 ± 14 SD</p> <p>Function – PRFEQ C2 Taken at baseline wk 0 = 27 ± 14 SD</p> <p>Taken at baseline wk 0 C2 wk 6 = 15 ± 14 SD</p> <p>Function – PRFEQ C1 Taken at baseline wk 0 = 3.8 ± 1.7 SD</p> <p>C1 wk 6 = 1.3 ± 1.8 SD</p> <p>Taken at baseline wk 0 C2 Taken at baseline wk 0 = 3.7 ± 1.7 SD</p> <p>= 22 kg ± 12 SD C2 wk 6 = 1.5 ± 1.6 SD</p> <p>Wk 6 = 26 kg ± 14 SD</p> <p>Grip-strength C1 Taken at baseline wk 0 = 17 kg ± 9.7 SD</p> <p>C1 wk 6 = 25 kg ± 12 SD</p> <p>C2 Taken at baseline wk 0 = 23 kg ± 15 SD</p> <p>SD :</p> <p>C2 wk 6 = 30 kg ± 17 SD</p>	6 week
There were no significantly different findings in the 3 groups after 6 weeks. The treatment approaches can be considered neither superior nor inferior to the other one as both were found effective.								

Manias & Stasinopoulos (Year : 2006)	A controlled clinical design trail (monocentre)	Con-Cryotherapy in form of ice bag was given after eccentric exercises (n=20)	No cryotherapy, only eccentric exercises (n=20)	4 weeks. 5 x per week	At week 0, 4 and 16 VAS measurement was taken)	In treatment group (exercise and ice) VAS at week 0=8.6 (initially 8.98 decreased to 8.22) VAS at 4 th week=1.7 (decreased from 2.41 to 0.99) VAS at 16 th week =1.5 (decreased from 2.06 to 0.94) There were no significantly different findings in the groups after 16 weeks. None of the treatment approaches can be considered as inferior to the other one as both were found effective.	In control group (exercise) VAS at week 0= 8.80(decreased from 9.25 to 8.35) VAS at 4 th week =1.9 (decreased from 2.72 to 1.08) VAS at 16 th week =1.6 (decreased from 2.37 to 0.83)	3 months	
Stasinopoulos & Stasinopoulos (Year : 2006)	75 (46, 39)	Controlled clinical design trail	Supervised exercise programme Eccentric exercises followed by stretching (n=25)	For control group C ₁ : Cyriax technique exercise (n=25) For control group C ₂ : Treatment with Bioptron light (n=25)	4 weeks 3 sessions in each week = 12 sessions	VAS for pain PFGS for function (at week 0, 4 th week, 8 th week, 16 th week, 28 th week)	Treatment Group Pain data: (out of 10) Taken at baseline wk :- 6.9 At 4 th wk :- 2.2 At 8 th wk :- 1.7 At 16 th wk :- 1.1 At 28 th wk :- 0.9 Function data: (out of 10) Taken at baseline week :- 3.9 At 4 th wk :- 7.8 At 8 th wk :- 8.2 At 16 th wk :- 8.3 At 28 th wk :- 8.4 For grip-strength Taken at baseline week :- 11.7 kgs At 4 th wk :- 33.4 kgs At 8 th wk :- 34.2 kgs At 16 th wk :- 34.7 kgs At 28 th wk :- 35.1 kgs	Control Group Pain data: (out of 10) C1:- Taken at baseline wk:- 6.9 C1:- At 4 th wk :- 2.8 C1:- At 8 th wk :- 2.6 C1:- At 16 th wk :- 2.4 C1:- At 28 th wk :- 1.9 C2:- Taken at baseline wk:- 7 C2:- At 4 th wk :- 3.3 C2:- At 8 th wk :- 3.0 C2:- At 16 th wk :- 2.8 C2:- At 28 th wk :- 2.6 Function data: (out of 10) C1 :- Taken at baseline wk :- 3.9 C1 :- At 4 th wk :- 7.1 C1:- At 8 th wk :- 7.3 C1:- At 16 th wk :- 7.6 C1:- At 28 th wk :- 7.8 C2:- Taken at baseline wk :- 3.9 C2:- At 4 th wk :- 6.7 C2:- At 8 th wk :- 7 C2:- At 16 th wk :- 7.2 C2:- At 28 th wk :- 7.3 For grip-strength C1:- Taken at baseline wk:- 11.7 kgs C1:- At 4 th wk :- 30.1 kgs C1:- At 8 th wk :- 30.5 kgs C1:- At 16 th wk :- 30.8 kgs C1:- At 28 th wk :- 31.29 kgs C2:- Taken at baseline wk:- 11.7 kgs C2:- At 4 th wk :- 28.6 kgs C2:- At 8 th wk :- 29.1 kgs C2:- At 16 th wk :- 29.6 kgs C2:- At 28 th wk :- 29.6 kgs	Week 4, 8, 16, 28
							Better improvement (p<0.05) was seen in case of supervised exercise programme (pain and function). Similar data were obtained for grip-strength for all groups		

Croisier <i>et al.</i> (Year:2007)	92 (36, 56)	Randomized controlled design trial	Eccentric exercises, massage with deep friction, US, ice & TENS, stretches (n=46)	Massage with deep friction, US, ice & stretches (n=46)	9 weeks 3X per weeks	For pain: VAS pain, Muscle strength For function: Disability questionnaire (week 0, 4 th week, 7 th week & 9 th week)	In T ₁ For pain Taken at baseline= 6.9±0.5 SD At the conclusion(9 th week) of treatment = 1.2±0.9 SD (p<0.05)	In T ₂ For pain Taken at baseline =6.7±1.5 SD At 9 th week =4.3±1.6 SD (p<0.01)	Week 0,4,7 and 9
						Results depicted significantly comparative improved outcomes in the eccentric treatment group. Tendon image enhancement in experimental: control group = 48%:28% Disability status improvement in experimental: control group = 74%:24%			
Nagraleet <i>al.</i> (Year:2009)	60 (18, 42)	Randomized Clinical design trial	Eccentric programme coupled with phonophoresis (5 min) (n=30)	Cyriax technique (n=30)	4 weeks 3 sessions in each week	For pain:VAS For function:Tennis Elbow Function Scale, and for grip-strength:Pain-free grip strength (week 0, 2 nd week, 4 th week & 8 th week)	Treatment group In case of pain (out of 10) Taken at baseline: -8.1 At wk0 :-7.03 At 2 nd wk :-5.6 At 4 th wk :-4.3 At 8 th wk :-5.6 In case of function (out of 40) Taken at baseline: -33.1 At 2 nd wk :-18.1 At 4 th wk :-9.1 At 8 th wk :-12.7 In case of grip-strength Taken at baseline: -16.5 At wk0 :-11.0 At 2 nd wk :-15.6 At 4 th wk :-20.5 At 8 th wk :-19.0	Control group In case of pain (out of 10) Taken at baseline: -8.2 At wk0 :-6.8 At 2 nd wk =4.9 At 4 th wk :-2.6 At 8 th wk :-3.2 In case of function (out of 40) Taken at baseline: -33.7 At wk0 :-27.3 At 2 nd wk :-18.1 At 4 th wk :-9.1 At 8 th wk :-12.7 In case of grip-strength Taken at baseline: -16.5 kgs At wk0 :-11.0 kgs At 2 nd wk :-15.6 kgs At 4 th wk :-20.5 kgs At 8 th wk :-19.0 kgs	Week 0,2,4 and 8 week
Cyriax group obtained better results in the follow-up periods (p<0.05).Marked improvement was obtained in both groups for all outcome procedures.									

Tyler <i>et al.</i> (Year:2010)	21 (10,11)	Prospective Randomized design trial	Eccentric exercises followed by stretching, heat, massage, US, ice-therapy (n=11)	Isotonic strengthening for wrist extensors followed by stretching, heat, massage, US, ice-therapy (n=10)	1 session per week for 7 weeks	For 7 days VAS, DASH, strength testing (at week 0, 7th week)	In case of pain (Out of 10) 6.7/10±2.8 SD: Baseline 1.3±2.7 SD: 7 th wk In case of function (out of 100) 38±30 SD: Baseline 33±22 SD: 7 th wk In case of or grip-strength deficit 20±16 SD: Baseline 17±18 SD: 7 th wk The size of effect : 0.5, 0.2 and 0.2 for pain, function and grip-strength respectively	Control group In case of pain (Out of 10) 6.3±2.8 SD: Baseline 4.9±2.7 SD: 7 th wk In case of function (out of 100) 38±30 SD: Baseline 33±22 SD: 7 th wk In case of or grip-strength deficit 20±16 SD: Baseline 17±18 SD: 7 th wk The size of effect : 0.5, 0.2 and 0.2 for pain, function and grip-strength respectively	Week 0 and 7
Wen <i>et al.</i> (Year:2011)	28 (15,13)	Prospective randomized controlled design trial	Eccentric programme (n=14)	Isotonic strengthening for wrist extensors followed by stretching, heat, massage, US, ice-therapy (n=10)	In first 2 weeks: 2X per week, after 1 week through-out 12 weeks	For 2 weeks VAS (week 0, 4 th , 8 th , 12 th and 16 th week)	In case of pain (Out of 10) 6.7/10±2.8 SD: Baseline 1.3±2.7 SD: 7 th wk In case of function (out of 100) 38±30 SD: Baseline 33±22 SD: 7 th wk In case of or grip-strength deficit 20±16 SD: Baseline 17±18 SD: 7 th wk The size of effect : 0.5, 0.2 and 0.2 for pain, function and grip-strength respectively	Control Group In case of VAS(out of 100mm) Mean baseline score =61 ±19 SD Mean baseline score =63 ±19 SD Mean pain duration = 85.9 days ±42.8 SD At 4 th wk: 27	Week 0,4,8,12 and 16
Söderberg <i>et al.</i> (Year:2012)	42 (18,24)	Randomized controlled design trial	Eccentric exercises and forearm band therapy (n=20)	Warm-up exercises for wrist and forearm band therapy (n=22)	2 x 8-12 repetitions of the wrist and forearm band therapy	For 8-12 weeks VAS (week 0, 4 th , 8 th , 12 th and 16 th week)	In case of pain (Out of 10) 6.7/10±2.8 SD: Baseline 1.3±2.7 SD: 7 th wk In case of function (out of 100) 38±30 SD: Baseline 33±22 SD: 7 th wk In case of or grip-strength deficit 20±16 SD: Baseline 17±18 SD: 7 th wk The size of effect : 0.5, 0.2 and 0.2 for pain, function and grip-strength respectively	Control group Average pain (0-100mm) VAS At baseline: 32 At 3 rd week: 20 At 6 th week: 6 Average pain-free grip-strength (Pa) At baseline: 50000 At 3 rd week: 53000 At 6 th week: 57000 Average wrist extensor isometric strength (kgs) Taken at baseline: 6.0 At 3 rd week: 6.5 At 6 th week: 6.2	Week 0,3 and 6

Thomas and Caroline (Year: 2015)	107 participants Affected elbows =113	Randomized controlled design trial	Astym (n=57)	Control group was administered eccentric exercises (n=56)	DASH questionnaire, For Grip strength: MGS	Treatments were given for 4 weeks, exercises this was followed with 4 weeks of confirmation period which didn't include treatment	Astym therapy resulted in statistically superior improvement as compared to the control group administered with eccentric exercises this was followed with 4 weeks of confirmation period which didn't include treatment Scores for DASH: $p=0.047$ Scores for MGS: $p=0.008$	At the 6 th month and at the 12 months
Wegener et al. (Year: 2016)	40 (12,28)	Randomized controlled design trial	For Treatment group 1: Eccentric exercise coupled with therapeutic elastic taping and (n=14) For Treatment group 2: Eccentric exercise coupled with sham taping (n=13)	Eccentric exercises (n=13)	PRTEE questionnaire, SF strength: PFGS, & Occupational Self-Assessment	Treatment was given throughout 12 weeks which included 4 sessions given weekly and 4 sessions given fortnightly	All the 3 groups improved in the outcome measures. But none of the outcomes measures showed any statistically significant dissimilarities when compared in the 3 groups	0,3 months
J. Nowotny et al (Year: 2018)	31	Randomized controlled design	Supervised eccentric exercise for wrist extensors	Supervised eccentric exercise along with wrist orthosis	Daily - 3 sessions/day Each session lasted for 10 min	PRTEE, Placzek score, VAS	PRTEE improved better in PT + orthosis group ($p=0.002$) Placzek Score reduced better in PT + orthosis group ($p=0.000$) VAS improved better in PT + orthosis group ($p=0.001$) After follow up they concluded that the elbow orthosis when used in unison with eccentric exercise produced better long term benefits.	12 weeks

VAS: Visual Analogue Scale; PFGS: Pain-free Grip Strength; DASH: Disabilities of the Arm, Shoulder and Hand; PRTEE: Patient-Rated Forearm Evaluation Questionnaire; SF-36: ; SD: Standard Deviation; wk: week; C: Control group; T: Treatment; US: Ultrasound; TENS: Transcutaneous Electrical Neuromuscular Stimulation; PT: Physiotherapy; MGS: Maximum Grip Strength
*Statistical significance: $p<0.05$

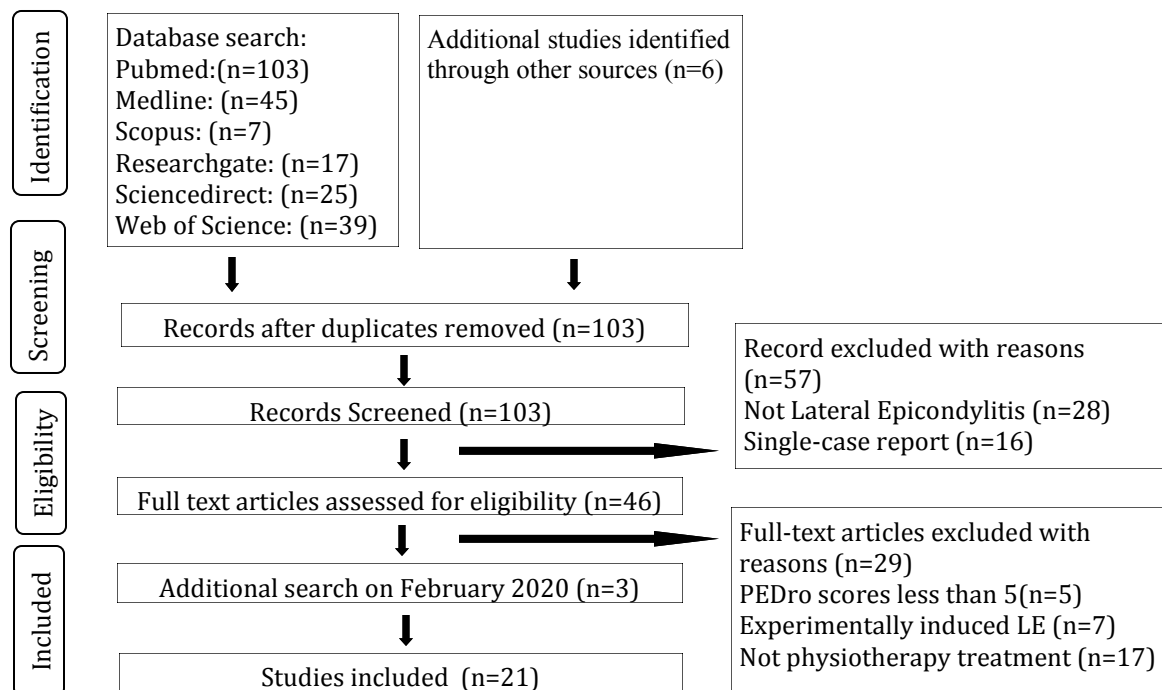
Table 3: PEDro table for mobilization-with-movement

Sl no	PEDro criterion	Vicen-zino	Ko-char	Pau ngm ali	Bis-set	Amro	Lau-rentius	Sa-har	Fra ncis co	Rey han
1.	Eligibility criteria were specified	1	1	1	1	1	1	1	1	1
2.	Subjects were randomly allocated to groups	1	1	1	1	0	1	1	1	1
3.	Allocation was concealed	0	0	1	1	0	0	0	1	1
4.	The groups were similar at baseline regarding the most important prognostic indicators	0	1	1	1	1	0	0	0	0
5.	There was blinding of all subjects	1	0	1	1	0	1	0	1	1
6.	There was blinding of all therapists who administered the therapy	0	0	0	0	0	0	0	0	0
7.	There was blinding of all assessors who measured at least one key outcome	1	0	1	1	0	0	0	0	0
8.	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	1	0	1	1	1	1	1	1	1
9.	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"	1	1	1	1	1	1	1	1	1
10.	The results of between-group statistical comparisons are reported for at least one key outcome	1	1	1	1	1	1	1	1	1
11.	The study provides both point measures and measures of variability for at least one key outcome	1	1	1	1	1	1	1	1	1
	Total	8	6	10	10	6	7	6	8	8

Table 4: PEDro table for eccentric exercise

SI No	PEDro criterion	Svernlöv	Martinez	Manias	Stasinopoulos	Croisier	Nagale	Tyler	Wen	Söderberg	Thomas	Wenger	J.Novotny
1.	Eligibility criteria were specified	1	1	1	1	1	1	1	1	1	1	1	1
2.	Subjects were randomly allocated to groups	1	1	0	0	1	1	1	1	1	1	1	1
3.	Allocation was concealed	0	0	0	0	1	0	0	0	0	1	1	0
4.	The groups were similar at baseline regarding the most important prognostic indicators	1	1	1	1	1	1	0	1	1	0	1	1
5.	There was blinding of all subjects	0	0	0	1	0	1	0	0	1	0	0	0
6.	There was blinding of all therapists who administered the therapy	0	0	0	0	0	0	0	0	0	0	0	0
7.	There was blinding of all assessors who measured at least one key outcome	0	0	0	1	0	1	1	1	0	1	0	0
8.	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	1	1	1	1	1	1	1	1	1	1	1	0
9.	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"	0	1	1	1	1	1	1	0	1	0	1	1
10.	The results of between-group statistical comparisons are reported for at least one key outcome	1	1	1	1	1	1	1	1	1	1	1	1
11.	The study provides both point measures and measures of variability for at least one key outcome	1	1	1	1	1	1	1	1	1	1	1	1
	Total PEDro score:	6	7	6	8	8	9	7	7	8	7	8	6

Figure 1: Outline of selection process of articles.



Discussion

This review was aimed at analyzing the literature on the effectiveness of widely used physiotherapeutic manual techniques for lateral epicondylitis, namely MWM and eccentric exercises. The overall data portrayed that in general, the two treatment approaches administered with/without conjunction with other treatment methods demonstrated good evidence for improving the state of lateral epicondylitis in the subjects.

Regarding the MWM therapy, in all the studies whether it was used alone or in conjunction with other treatment methods such as ultrasound (US), corticosteroid injection, taping, TENS, stretching, etc it excelled significantly than the control group/s. The dosage of MWM was administered as 3 sessions per week in most of the studies; however, a generalization could not be done concerning the duration of the exercise program. The adherence of patients to the treatment approach majorly depends on the appreciation of pain reduction, MWM was found to deliver immediate pain relief after the manipulation in almost all of the studies. In addition to this, subjects demonstrated improved grip strength and daily functional activities following the treatment completion, which can be considered as long-term benefits of this treatment approach. It is interesting to know that Nikolaos et al (2018) have published a meta-analysis of studies

performed using mobilization-with-movement on peripheral joints including 16 studies with 576 subjects taken between 2008-2017, they found clinically significant statistical scores in their study and they added that further validation in this technique is warranted.⁶²

In the case of eccentric exercises for lateral epicondylitis, we finalized a larger number of studies (n=12). So the results also showed a greater variation as compared to studies that included MWM. In an exception to two studies,^{57,59} the remaining ten studies have coupled eccentric exercises with other treatment approaches which caused difficulty in pooling the data. The evidence regarding the superiority of this approach against other approaches remains unclear, the results of five studies showed no statistically significant differences between treatment and control group where eccentric exercise was used in combination with ice/sham taping/ US, TENS, iontophoresis, Astym and/or wrist orthosis. Our findings are consistent with the review study performed by Ortega-Castillo⁶³ who concluded in their study that although eccentric exercises produce improvement in grip strength and pain reduction for upper limb tendinopathies, the evidence is questionable to consider it as a superior treatment to other approaches. This study was unable to generalize the exercise protocol design for eccentric exercise; the number of repetitions per set, sessions per week, rest

interval between sets, intensity, and progression of weight addition varied from one study to the other. Hence, ideal parameters for repeatability of research could not be established. Raman J et al⁶⁴ produced similar findings in their study demonstrating beneficial findings of eccentric exercises in LE, but the need for optimal dosage protocol remains undefined. Nevertheless, all of the studies which investigated the use of eccentric exercises showed improvement in the patient's ailment when compared with baseline readings; they were able to produce beneficial effects on grounds of pain, grip strength, and functional questionnaires.

Potential risk of bias in the review process

The absence of a follow-up period in four of the studies complicates the comparison between the studies;⁴⁵⁻⁴⁸ this condition can be seen in form of both acute and chronic cases, however, this review study did not generalize the individual studies based on these criteria. The efficacies of both approaches were tested against the control group/s which included other treatment approaches or no treatment, but these approaches were not tested against each other in any of the studies.

Conclusion

This review study has generated a sufficient level of evidence for both the treatment approaches showing beneficial results in the subjects with lateral epicondylitis. In particular, MWM can be recommended for patients demanding rapid results since; in few studies, it has shown comparatively immediate after-treatment positive results with long-term benefits. Although eccentric exercises didn't excel than the control group/s in more than half of the studies, we do not discourage its application as it has shown remarkable improvement in the subjects when utilized singularly and its benefits are amplified when it is incorporated along with other treatment methods. As the condition is often encountered as chronic cases in most of the patients and keeping in mind the chances of recurrence, the exercises have to be accompanied by follow-ups to ensure that the benefits of the effects of the treatment are long-lasting.

The studies included in the review consisted of treatment approaches administered to subjects irrespective of the type of activities that they were involved in (tennis, cricket, carpenters, housewives, typists, construction workers, and so on).

Implications for further research

This review process showed only two randomized controlled studies^{43,47} which incorporated both MWM along with eccentric exercises for the

treatment of LE. Future randomized controlled trials which include the application of both these treatment approaches in unison might give better answers to the establishment of efficient therapies for LE. Wherever possible, blinding of the assessors should be implicated. Future studies should also put light on conducting separate studies for the acute cases and chronic cases including appropriate follow-up periods which helps to generate short-term and long-term results.

The trend of racquet sports has been increasing tremendously in the past few years, lateral epicondylitis is a common condition faced by such individuals. We didn't encounter any reliable articles which could provide evidence for the utilization of these therapies in isolation with sportspersons. Keeping in mind that those people who are into sports have the necessity of rapid recovery, the upcoming studies should isolate the studies on the treatment approaches for sportspersons as it would be very beneficial for them to "return-to-sport" in a lesser time span. On-site treatment programs have proved beneficial⁶⁵ that can additionally provide therapist-supervised protocol directed in favor of the sportsperson and these can be encouraged during rehabilitation.

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Contribution of authors

RM and SH conceived the study, coordinated and contributed to design the study. RM contributed to the extraction of data, synthesis of evidence, incorporated the relevant feedback, and drafted the final manuscript. SH contributed to the extraction of data, performed the necessary editing, and listed suggestions for improving the design, interpreting the findings, and revised the final manuscript.

The final manuscript has been read and approved by all the authors.

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