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Elbow Mobilization With Movement (MWM)

Review article

Efficacy of Mobilization With Movement (MWM) in Lateral Epicondylalgia: Role of Pain Mechanisms- a Narrative Review.

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ABSTRACT

Background and objectives: Lateral Epicondylalgia (LE) is one of the most common repetitive strain injuries. Though various pharmacological and non pharmacological management strategies for LE have been described, there is paucity of high level evidence supporting their effectiveness. Mobilization with Movement (MWM) is a group of manual therapy techniques which claim to provide immediate pain free improvement of range of motion and functional activities. This review aims to explore the pain mechanisms underlying LE, the mechanisms underlying the effect of MWM and the clinical studies looking into effectiveness of MWM in LE.

Search strategy – A comprehensive search was carried out on the following electronic databases – PubMed, CINAHL, AMED, Web of Science, ScienceDirect, Cochrane Database of Clinical Trials, EMBASE. The date restrictions from January 1992 till present were applied. The search terms used were 'Mobilization', 'Mulligan's, 'MWM', 'Mobilization with movement', 'tennis elbow', 'lateral epicondylalgia', 'lateral epicondylitis', 'pain mechanisms'.

Selection Criteria: Randomized control trials assessing the effectiveness of MWM in LE, diagnostic studies assessing the pain mechanisms in LE and studies examining the effects of MWM were included. Case series, single case studies, unpublished reports were not included.

Data Collection & Analysis: Studies were divided into three categories – diagnostic studies for assessing the pain mechanisms in LE, Studies examining the mechanisms for the effectiveness of MWM and Clinical studies on the effectiveness of MWM in LE.

Results: The review indicates that degeneration plays a major role in the presentation of LE, while inflammatory component has not been found in any of the biopsy studies. MWM produces an endogenous opioid mediated form of analgesia. The clinical studies have shown that there is a significant immediate hypoalgesic effect of MWM in LE.

Key words: lateral elbow pain, physiotherapy, manual therapy, Mulligan's concept, pain sciences.

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INTRODUCTION

Lateral elbow pain, first described by Runge in 1873, has been known with different terms such as tennis elbow, epicondylosis, lateral epicondylitis, lateral elbow pain and epicondylalgia.[1,2]

Lateral epicondylalgia (LE) is a clinical diagnosis based on a presentation of tenderness over the common extensor origin (CEO) and pain exacerbated by repeated wrist extensions.[3] The history commonly includes forceful and repetitive gripping and painful weakness in the gripping activities.[4]

The prevalence of LE in general population is about 1-3% between 30 and 64 years of age,[3,5] with the peak incidence between 45 and 54.[2] It seems to affect both males and females equally,[6-8] though Stasinopoulos and Johnson[9] postulated that it can be more severe and longer lasting in females than in males. There is wide disparity in reported prevalence in occupational populations varying from 2-23%.[10-12] These have been attributed to varying definitions; self reported

measures and difference in clinical examination techniques.[13]

Though various pharmacological (NSAIDS, corticosteroid injections) and non pharmacological (ultrasound, stretching, strengthening, acupuncture, LASER, extra corporeal shock wave therapy, orthotics) management strategies for LE have been described, there is paucity of high level evidence supporting their effectiveness.[14-21]

Mobilizations with movement (MWM) are a group of manual therapy techniques which claim to provide immediate reduction in pain and improvement in function, if indicated [22-24]. A MWM technique for LE involving a lateral glide to the proximal forearm with the distal humerus fixed has been described in the literature (See Appendix VI)[25-28]. Many reviews have looked into the effectiveness of manual therapy and physiotherapy in the management of LE, but none has specifically examined the role of MWM in LE[14-16, 18-21,42]

Traditionally LE has been thought of as an inflammatory process of the common extensor origin, but recent findings have challenged this belief[31]. Thus it is imperative that a review of the diagnostic studies is carried out to understand the possible pain mechanisms underlying the presentation of LE.

AIMS OF THE REVIEW -

This papers aims to provide insight into the efficacy of MWM in LE.

The specific objectives of this review are –

- Explore the pain mechanisms underlying the presentation of LE.
- Examine the postulated mechanisms for the effectiveness of MWM.
- Appraise the literature concerning the effectiveness of MWM in LE.
- Determine the clinical relevance of the research so as to help assist clinical decision making in LE.
- Identify the gaps in literature to develop recommendations for future research.

METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW -

Types of studies: The following study designs will be included in the review:

- Randomized controlled trials (RCTs)
- Controlled clinical trials (CCTs) (includes quasi-randomized and controlled before-after designs)

Designs not included in this review are: cohort; case-control; single case studies; single subject; case series; and pre/post studies with no control group.

Types of participants: The review will include adults with a clinical diagnosis of LE as confirmed by presentation of tenderness over the common extensor origin (CEO) and pain exacerbated by repeated wrist extensions[3].

Types of interventions: Diagnostic studies using standardised approaches like microdialysis or biopsy to assess the presence of inflammatory markers were included for the first section of the review. Studies examining the effect of MWM compared to placebo control or to other interventions were included in the next sections of the review.

Type of Outcomes: The primary outcomes of interest included presence of inflammatory markers e.g PGE2 or signs of other pathological processes. In addition, for the clinical studies, the principal outcome of interest was pain free grip strength (PFG) and pressure pain threshold (PPT).

SEARCH STRATEGY

A comprehensive search was carried out on the following electronic databases – PubMed, CINAHL, AMED, Web of Science, ScienceDirect, Cochrane Database of Clinical Trials, EMBASE. The date restrictions from January 1992 till present were applied. English language published papers were considered for this review. Unpublished reports, dissertation articles, anecdotal evidence was not included.

The search terms used were 'Mobilization', 'Mulligan's, 'MWM', 'Mobilization with movement', 'tennis elbow', 'lateral epicondylalgia', 'lateral epicondylitis', 'pain mechanisms'. These were combined using the Boolean operators like AND, OR, NOT. Apart from that, reference lists of the retrieved articles were scanned for additional articles and the bibliographies of the renowned authors in the field were also searched on the internet to ensure that all the relevant articles were included in the review.

STUDY SELECTION

In the preliminary screening of studies, any articles mentioning the search terms were retrieved. The title and abstract of the selected articles were reviewed and compared against the inclusion criteria. If a study clearly did not fulfil the criteria, it was excluded, else retained for the next round of screening. The full text of the remaining studies were retrieved and screened against the inclusion and exclusion criteria.

DATA COLLECTION & SYNTHESIS

The included papers were reviewed in full and were categorized into studies examining the pain mechanisms of LE, studies examining the mechanisms for the effectiveness of MWM and clinical studies on the effectiveness of MWM in LE. A qualitative narrative approach to reviewing was chosen due to the heterogeneous nature of study designs, which disallowed a systematic quantitative review and pooling of results [29]. Qualitative summarizing of studies using levels of evidence and levels of recommendations by Center for Evidence Based Medicine (CEBM), Appendix VI, has allowed the author to draw conclusions from this review and present implications for clinical practice and research. Level I studies produce results from which definitive conclusions can be made. Level II thru level IV studies report progressively less credible evidence from which only cautious conclusions can be drawn. No definite conclusions can be made from level V evidence.

RESULTS

Selection of Studies: A total of 13 studies were included in this review of which five diagnostic studies examined the underlying pathobiological mechanisms in LE, while four studies assessed the mechanisms of effectiveness of MWM and four clinical studies investigated the effectiveness of MWM in LE. The initial electronic database search yielded 732 articles. After adjusting for duplicates, 679 remained. Of these, the initial review of titles and abstracts excluded 648 studies due to not fulfilling the exclusion and inclusion criteria. Four studies were discarded as the full text article could not be obtained. Full text articles of the remaining 27 articles were carefully reviewed and matched against the criteria set out above. It appeared that 11 studies fulfilled the criteria and were included in this review. In addition, a scan of the references led to further two more studies being retrieved, which were included in the review. The PRISMA flowchart is presented in Flowchart 1 below.

Study Characteristics

Studies Examining the role of inflammation in LE

The five studies selected for review are all controlled trials which looked for the presence of inflammatory markers to identify the possible role of inflammation in the presentation of LE. Four of these[32-35] used muscle biopsies while the fifth by Alfredson[31] also used microdialysis technique. The characteristics of these studies are presented in Table I and have been described in detail in Appendix I.

All of the studies cited in table 1 have shown the absence of inflammatory cells in the biopsies except Uchio et al [35], which has shown some involvement of neurogenic inflammation which leads to vasodilatation and extravasation of plasma fluid. However, use of different histopathological techniques and immunochemical markers, patients in varying stages of the condition,age ranges and very small sample sizes prevent any strong conclusions being drawn [31-35]. The presence of hypervascularity, increased fibroblasts, evidence of necrosis and/or calcification is strongly indicative of degenerative tendinosis, which is consistent with the findings

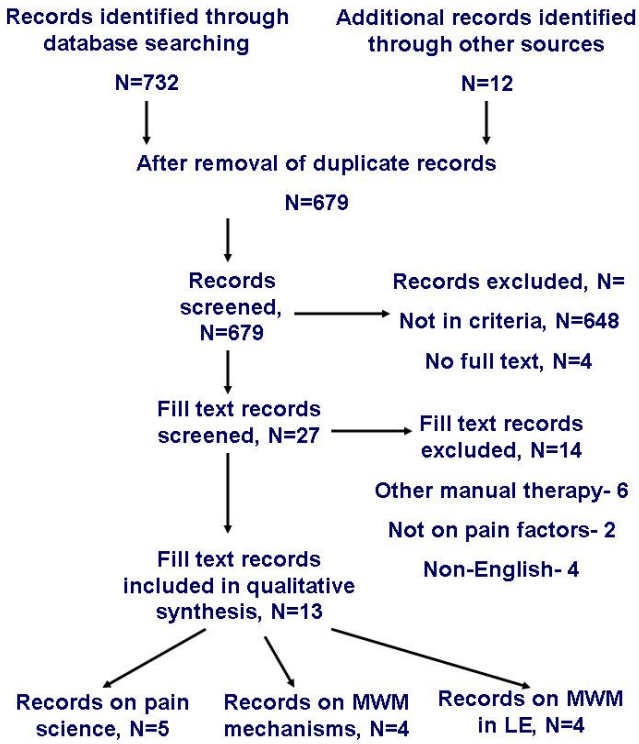

FIGURE-1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of study methodology

at Achilles and the patellar tendon.[36] Alfredson et al[31] using micro-dialysis found a high concentration of glutamate (an excitatory neuro transmitter) in the patients with LE. Based on this, it has been proposed that altered afferent neuronal output may be an important factor in causation of LE. Though using a small sample size, the measures adopted to ensure accuracy of results may allow extrapolation of results to general LE populations.

Even though there is lack of strong evidence, the results of these studies indicate that degeneration plays a major role in the presentation of LE, while an inflammatory component has not been found in any of the biopsy studies . Based on these findings, use of conventional measures like NSAIDs and corticosteroids, have been challenged for the pain relief in LE.[37]

An important aspect which has to be considered is the use of chronic LE subjects in all the studies discussed above. This could be an important factor explaining the absence of any inflammatory substances in the biopsy samples.

2. Studies exploring the mechanisms of effectiveness of MWM –

Four pain science studies were found that explored the mechanism of pain alleviation by MWM for LE [38-41]. These have been described in detail in Appendix II, while a comparison between them is made in table II, presented below.

Paungamali[38] analysed the physiological effects of MWM by measuring the changes in pain and sympathetic nervous system (SNS) function in chronic LE. Their repeated measures, placebo controlled design, use of validated outcome measures, adequate sample size lend validity to the results of this trial, which showed a significant hypoalgesic effect and sympathoexcitatory effects, and are similar to the one observed in manipulation also [27,28]. On the basis of this pattern, the authors have postulated that MWM may activate some centers in the neuraxis and the involvement of endogenous opioids in these effects.

In a similar study, Paungamali et al[39] used naloxone antagonism to assess the nature of the analgesic effect obtained. They used a repeated measures design to assess whether tolerance was exhibited to repeated doses of naloxone and found that the hypoalgesic effect of MWM did not reduce with repeated sessions. With these results, authors concluded that endogenous opioid pain suppression system plays an important role in effects of MWM.

In another randomised, repeated measures, double blind, placebo controlled trial, Paungamali et al [40] found that naloxone did not significantly reduce the pain reduction

TABLE-1: STUDIES ON MECHANISM OF PAIN PRODUCTION IN LATERAL EPICONDYLALGIA (LE)

First Author	Design	Group	Diagnostic Technique	Results	Comments
Alfredson[31]	CCT	LE (n=4) Control (n=4)	Microdialysis and biopsy.	Higher conc. of glutamate in LE. No diff. In con. of PGE2.	No biochemical signs of inflammation. Potential excitatory neurotransmitter/ neurogenic role.
Ljung[32]	CCT	LE (n=20) Control (n=9)	Muscle Biopsy	Moth eaten fibres and fibre necrosis in the LE group and not in the control group.	Indicative of mechanical/metabolic overload, no inflammatory components found.
Ljung[33]	CCT	LE (n= 5) LE (n=4)	Muscle Biopsy	NK1-R immunoreactions at the lateral epicondyle in patients with LE. No inflammatory cell Infiltrates.	Possible neurogenic involvement in the pathophysiology of LE.
Potter[34]	CCT	LE (n=33) Surgical (20)	MR Imaging, Surgical debridement, biopsy	Degeneration of ECRB, disruption of collagen without inflammation.	Degenerative changes but no inflammatory component found.
Uchio[35]	CCT	LE (n=10)	Muscle Biopsy	Proliferation of fibroblasts associated with dense collagen fibers. Substance-p like immunoreactivity or CGRP-like immunoreactivity.	Neuropeptides and cytokines may promote inflammation and stimulate proliferation and matrix synthesis of fibroblasts.

CCT –Controlled Clinical trial, LE – Lateral Epicondylalgia, PGE2 - prostaglandin E2, NK1 r – Neurokinin 1 receptor, MR- Magnetic resonance, ECRB – Extensor carpi radialis brevis, CGRP - Calcitonin gene-related peptide.

effects of MWM over repeated administration. Based on these, they concluded that there may be non adrenergic, non opioid endogenous pain mechanism involved in the hypoalgesic effects of MWM. Their study design and use of stringent methodology lends validity to the results which can be questioned due to use of a sample size based on another study of 73% power.

In contrast to the above studies which found immediate hypoalgesic effects of MWM and concluded that non opioid endogenous form of analgesia is probably the underlying mechanism for its effectiveness, Slater et al [41] used an experimentally induced LE in 24 subjects allocated either to MWM or to the placebo group and found no significant difference between the two groups for visual analogue scale (VAS) or for any other factors. Thus the authors concluded that MWM does not activate analgesic mechanisms in experimentally induced LE.

From the above review it is clear that even though effects could not be shown in experimentally induced LE, MWM does produce significant hypoalgesic effects which seem to show endogenous opioid form of analgesia. Another aspect which needs to be considered is that all the studies cited above have been done by the same author

TABLE-2: STUDIES EXPLORING THE MECHANISMS OF EFFECTIVENESS OF MOBILIZATION WITH MOVEMENT (MWM)

Author	Design	Groups	Results	Comments
Paungamali[38]	Placebo controlled repeated measures	MWM, placebo , Control (N=18)	Increase PFG (48%) and PPT (15%), which were greater than placebo and control. Sympatho-excitation also occurred concurrently	Only short-term (immediate) effects were evaluated
Paungamali[39]	Placebo ,controlled ,repeated measures	MWM, placebo , Control (N=24)	45.29% increase in PFG 17.51% in PPT across all therapy sessions.	Hypoalgesia was non tolerant to repetition.
Paungamali[40]	Double blind RCT, placebo	Naloxone, Saline and Control delivered prior to the MWM (N=24)	Changes in outcome measures were not different from placebo and control conditions	Non-opioid-mediated hypoalgesia
Slater[41]	randomized, placebo-controlled	MWM group and control (N=24)	No significant difference between two groups for analgesia or for force augmentation.	Mechanisms by DOMS and saline-induced pain and effects of MWM do not match

RCT – Randomized controlled trial, PFG – Pain free grip strength, PPT – Pressure pain threshold, DOMS – Delayed Onset Muscle Soreness.

which could be a source of potential bias.

Clinical studies exploring the effectiveness of MWM in LE.

Four studies were found which evaluated the clinical effectiveness of MWM in LE. Their description is given in Appendix IV while a brief comparison is presented in Table III.

Bisset et al [42] in their pragmatic randomised control trial on 198 subjects compared MWM & exercise with corticosteroids and wait & see. They found that at 52 weeks, MWM with exercise was significantly better than both steroids and wait & see, though at 6 weeks steroids had a significantly better outcome than other two groups. Though a stringent methodology was used including power and sample size calculation, 52 weeks follow up, valid and reliable outcomes but use of exercise along with MWM makes it difficult to delineate the effects to MWM alone.

Abbott et al [26] in their single intervention pre & post design on 25 subjects with unilateral LE found significant reduction in pain and increase in pain free grip strength. Use of a single intervention design along with lack of any follow up prevent any strong conclusions of effectiveness to be drawn though it does present a glimpse of the immediate effects of MWM for pain relief and improvement in function.

Kocher and Dogra [43] compared the effects of MWM with ultrasound and control group in 66 patients. They found that MWM produced significant change in VAS, weight lift and grip strength compared to other groups, but use of ultrasound in MWM group and non randomisation of the control group affect the validity of the results. The results have not been detailed enough to help draw strong conclusion of effectiveness of MWM.

Vicenzino et al [28] evaluated the effectiveness of MWM compared to control and placebo conditions on 24 subjects in their repeated measures design. They found a significant change in pain free grip strength and pressure pain threshold only on the affected side in MWM group. The same effect was not observed in the other two

groups. A strong study design illustrates the immediate effects of MWM though long term effects were not considered. Thus from the above studies it is clear that there is some evidence to show the immediate pain relieving effects of MWM which may enhance return to function, though the long term effects have not been evaluated alone in any research.

DISCUSSION

In this review, the author has explored the pain science studies to evaluate the mechanisms involved in production of pain in LE along with the mechanism of effectiveness of MWM and the clinical studies to consider the efficacy of MWM in reduction of pain and improvement in function.

The pain science studies have shown that LE may predominantly present as a degenerative, overuse condition rather than an inflammatory condition [31-35] (Level of evidence 2b). Similar findings have also been shown at patellar and Achilles tendons [36,44].

TABLE-3: CLINICAL STUDIES EXPLORING THE EFFECTIVENESS OF MWM IN LE.

Author	Design	Treatment groups	Outcome measures	Results	Comments
Bisset[42]	Single Blind RCT	MWM + Ex (66) Injections (65), Wait & See (67)	Global Improvement, Grip Force, Assessor severity rating.	At 6 weeks- Injection (78%) better than physiotherapy (65%) & wait & see (27%). At 52 weeks- Physiotherapy better than injections & wait& see.	Other physiotherapy was also used making it difficult to delineate the effects of MWM. Discrepancy in No. of Rx sessions.
Abbott [26]	Single pre post design	MWM (25)	Pain, pain free grip strength, maximum grip strength	92% had decrease in pain, 17% had increase in PFG, 5% had increase in MGS	Single intervention, Convenient sampling and single session compromise the reliability of results.
Kochar[43]	Randomised control trial	MWM+ UST(23), UST alone (23), No treatment (20).	VAS, weight test, grip strength, patient assessment	On all parameters, MWM group was significantly better than UST which was better than no treatment.	The No-treatment group was not randomised. No placebo group No Long term follow up.
Vicenzino[28]	Double Blind RCT	MWM, Placebo, No Rx (n=24)	Pain free grip strength, pressure pain threshold.	Increase PFG (46%) and PPT (10%), which were greater than placebo and control conditions	No long term effects were studied

RCT – Randomized control trial, PFG – Pain free grip strength, MGS – Maximum grip strength, UST – Ultrasound Therapy, PPT – Pressure pain threshold, Rx - Treatment

Khan et al[45] have proposed that in cases of degenerative tendinosis, active movement play an important role in rehabilitation to function while similarly, in a clinical commentary, Vicenzino et al[46] have reviewed that mobilization/manipulation alone are also effective in the degenerative tendinosis of extensor carpi radialis brevis which is the main tendon affected in LE.

MWM combines the use of active motion and passive manual mobilization techniques in the form of repeated gripping and sustained lateral glide to elbow. Both these techniques have been shown to be individually effective in LE. [47,48] Thus, the theoretical rationale for effectiveness of MWM in LE seems to be well favoured.

Previously spinal manipulation has shown to have immediate hypoalgesic effects combined with significant sympatho-excitatory response [49, 50]. Similar results have also been achieved with MWM.[5,38,50-53] This hypoalgesic effect has been shown to be non opioid in nature through the naloxone blockade studies in LE and other conditions[54-6,38,39]. In an animal study, Skyba et al [57] showed that the substrates for hypoalgesic effect included both serotonergic and norepinephric pain inhibition systems. Based on the results of the review of studies above and also taking into consideration the animal study, it is safe to assume that MWM and manipulation both exert their effects through a non opioid, endogenous pain pathway.

With regards to the clinical studies, all of the studies reported immediate reduction in pain and increase in the pain free grip strength. The pain relieving effect was found only on the affected side [28], which is in agreement with the Mulligan's original positional fault hypothesis.[25] This hypothesis postulates that in a chronic dysfunction, a mechanical alteration is produced leading to joint dysfunction and pain and if that is corrected by the use of appropriately directed mobilization, it can produce an immediate pain relief and return to function. This theory however differs from other studies on manipulative therapy which have shown results even in asymptomatic subjects [27].

Stratford et al [57] had reported maximum grip strength (MGS) to be most responsive measure of strength in LE but the studies on MWM showed that pain free grip strength is a better predictor of outcome as it showed significantly better improvement than MGS [42, 43, 26, 28].

Through this review, it is clear that degenerative rather than inflammatory mechanisms play a major role in the pathogenesis of LE (Level of evidence 2a) and MWM produces a non opioid form of analgesia in LE to produce an immediate reduction in pain and improvement in function which is characterised by significant increase in pain free grip strength, though this effect was not observed in experimentally produced LE [41] (Level of evidence 2a).

The author's clinical experience of working with LE patients has shown that MWM presents a useful clinical tool for a physiotherapist in reducing the number of sessions by quicker return to function even in recalcitrant cases.

The trials in this review have been analysed qualitatively as the data is statistically and clinically heterogeneous [58]. Though satisfactory in the methodological rigour, there were some short comings for the studies included in this review. The most important of them being lack of any follow up of the effects. Only one study analysed the effect at 52 weeks time and found that there was significant effect of MWM and exercise when compared to wait and see, though not significantly better than corticosteroids. Another issue is the use of experimental conditions in the pain science studies which doesn't take into consideration the clinical co – morbidities associated with a condition.

Thus this review presents some useful insight into the pain mechanisms underlying LE, the clinical effectiveness of MWM and some postulations as to the probable mechanisms of its effectiveness.

Implications for Research

Future research should include high quality RCTs with longer follow up with validated outcome measures to confirm the clinical effectiveness of MWM in LE. Apart from that, further research is also needed to confirm the

neurophysiological effects of MWM. The positional fault hypothesis needs to be tested using high quality MRI studies. Based on such research an effective evidence based clinical practice can be formed for MWM in LE.

Implications for clinical practice

As discussed above, there is a level 2a evidence of immediate hypoalgesic effect of MWM in management of clinical symptoms of LE. In addition, there is a valid theoretical rationale for the use of MWM in management of LE, as explained in the discussion above. Thus along with other modalities, MWM can form a valuable tool for non conservative management of LE.

CONCLUSION

This review has presented evidence to prove that degeneration is the patho-biological mechanism in production of the symptoms of LE. In the studies exploring the pain-relieving effects of MWM, an endogenous, non opioid form of analgesia was found to play a predominant part in the pain alleviating effects. The studies on clinical efficacy of MWM found an immediate reduction in pain and improvement in function in patients with LE. The major limitation was the assessment of only the immediate effects; no attempt was made to assess the long term effects. Clinical and research implications have been presented.

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APPENDIX-1: STUDIES ON PAIN SCIENCES IN LATERAL EPICONDYLALGIA (LE)

Study	**Alfredson**[31]
Methods	Controlled trial Randomisation: No randomisation Blinding: No blinding Sample size Calculation: Not reported Appropriate statistical analysis: Mean concentrations of PGE2 were compared between two groups.
Participants	8 participants (4 in each group) Inclusion Criteria: For experimental group, pain and tenderness more than 6 months from ECRB origin and be on waiting list for surgical treatment. For control group, healthy adult subjects with no history of lateral elbow pain. Exclusion Criteria: For experimental group other related differential diagnoses were excluded through clinical examination.
Interventions	Microdialysis. A local anaesthetic was injected into skin and subcutaneous tissue. Skin incision was made and microdialysis catheter was inserted. Sampling was done every 15 minutes.
Outcomes	Mean concentrations of glutamate and PGE2 in ECRB and normal tendons were compared.

Study	**Potter**[32]
Methods	Correlation study Randomisation : Not reported Blinding: Assessors Sample size calculation: Not reported. Appropriate Statistical Analyses: Comparison was made between the MR imaging, surgical findings and histopathological findings.
Participants	33 participants Inclusion criteria: Patients with chronic tennis elbow, having undergone a trial of conservative management. Exclusion criteria: Professional athletes, corticosteroid injection within last 3 months.
Interventions	MR Imaging, surgical debridement/ tendon release, histopathological analysis
Outcomes	Correlation between the three techniques, no statistical analyses reported.

Study	Ljung[33]
Methods	CCT Randomisation: None Blinding: Assessors Sample size calculation: not reported Statistical analyses: One-way ANOVA to compare the different tissue types.
Participants	20 patients Inclusion criteria: Chronic tennis elbow, trial of conservative management. Exclusion criteria: Other differential diagnoses such as synovitis, 5 healthy volunteers and 5 autopsies: No history of TE.
Interventions	Muscle biopsies were taken 5-10 cm below the lateral epicondyle and histological analyses performed.
Outcomes	The fibre type and its distribution was analysed using one way ANOVA.

Study	Ljung[34]
Methods	CCT, observational Randomisation: None Blinding: Not applicable Sample size: Small , convenient sample Appropriate statistical Analyses: Observational
Participants	Nine patients: 4 for medial epicondylitis (ME) and 5 for tennis elbow. Inclusion criteria: Surgery for ME or TE.
Interventions	Immunohistochemistry and antibodies to substance P and CGRP and PGP 9.5 were studied.
Outcomes	Morphological correlate for occurrence of nerve mediated effects in this region

Study	Uchio[35]
Methods	CCT Randomisation: Not applicable Blinding: none Statistical analyses: simple regression analyses to assess the relation between the immunoreactives of neuropeptides.
Participants	9 patients Inclusion criteria - Chronic TE, having undergone a trial of conservative management.. Exclusion: Differential diagnoses like synovitis.
Interventions	Biopsy to perform immunohistochemistry and immunostaining.
Outcomes	The immunoreactivities of substance P, CGRP,IL-1, and TGF-1 with biopsy.

Review article

APPENDIX-2

STUDIES ON MOBILIZATION WITH MOVEMENT (MWM) AND PAIN IN LATERAL EPICONDYLALGIA (LE)

Study	**Paungamali[38]**
Methods	Repeated measures design Randomisation: Not applicable Blinding: None Sample size- Adequate (based on previous research) Statistical Analyses: Between sessions comparison
Participants	24 patients Inclusion Criteria: Chronic tennis elbow. Exclusion criteria: cervical or upper limb problems, other related differential diagnoses and previous manipulation of elbow.
Interventions	6 sessions of MWM were applied to TE on all the 24 subjects.
Outcomes	Pain threshold measures consisting of PFGS and PPT.

Study	**Paugamali[39]**
Methods	A placebo, control, repeated-measures design Randomisation: Not applicable Blinding: None Sample size: Calculation based on pilot study. Statistical analyses: two-way within-subject ANOVA to assess pre and post treatment readings.
Participants	24 subjects Inclusion Criteria: Unilateral TE Exclusion criteria: Any other related disorder of cervical spine or upper limb, previous therapy for elbow pain.
Interventions	MWM – 10 repetitions Placebo – 10 repetitions Control – No manual force.
Outcomes	Pain Related measures– PFG, PPT, TPT SNS indicators– cutaneous blood flow, skin conductance, skin temperature, blood pressure and heart rate.

Study	**Paungamali[40]**
Methods	Randomised cross-over controlled trial Randomisation: Adequate Blinding: Double blinding Sample size –based on previous research Statistical analyses – One way ANOVA
Participants	18 subjects Inclusion criteria: chronic unlilateral TE. Exclusion criteria: cited from previous studies.
Interventions	Participants were administered naloxone, saline or control. MWM was given daily according to the protocol described.
Outcomes	PFGS,PPT,TPT

Study	**Slater [41]**
Methods	Randomised placebo-controlled design Randomisation: adequate Blinding: not described Sample size: not described Statistical Analyses: two way repeated measures ANOVA to compare the group difference pre and post intervention.
Participants	12 subjects in each group Inclusion criteria: Normal healthy subjects without any history of elbow pain.
Interventions	Experimental TE produced through saline and DOMS. Then one group was given MWM while other was used as a control.
Outcomes	VAS and PPT

APPENDIX-3

CLINICAL STUDIES ON MOBILIZATION WITH MOVEMENT (MWM) IN LATERAL EPICONDYLALGIA (LE)

Study	**Abbott [42]**
Methods	Design: One group pre post test design Randomisation : Not applicable Blinding : not applicable Sample size : not described Statistical Analysis : one tailed t test was used to compare means.
Participants	Twenty five subjects Inclusion criteria: clinical diagnosis of TE Exclusion criteria: any other co existing health condition, previous treatment with manipulation.
Interventions	Single intervention of MWM
Outcomes	pain with active motion, (2) pain-free grip strength and, (3) maximum grip strength

Study	**Bisset [26]**
Methods	Design: single-blind randomised controlled trial Randomisation : Adequate Blinding : assessor blinding Sample size : calculation described Statistical Analysis: means of the change in outcome measure were compared using the intention to treat analysis.
Participants	198 participants aged 18 to 65 years with a clinical diagnosis of tennis elbow of a minimum six weeks' duration, who had not received any other active treatment by a health practitioner in the previous six months.
Interventions	Eight sessions of physiotherapy; corticosteroid injections; or wait and see.
Outcomes	Global improvement, grip force, and assessor's rating of severity measured at baseline, six weeks, and 52 weeks.

Study	**Kocher [43]**
Methods	Design: randomised controlled trial Randomisation: into two experimental groups but not for the control group Blinding: adequate assessor blinding Sample size: Not calculated Statistical Analysis: One way ANOVA for within group and two way ANOVA for between group analysis.
Participants	66 patients Inclusion criteria: clinical diagnosis of TE Exclusion criteria: concomitant conditions and any previous treatment in 3 weeks.
Interventions	MWM and ultrasound, ultrasound only and control group. All the groups then followed up with exercises following the experimental period of 10 sessions in three weeks.
Outcomes	VAS, weight test and PFGS

Study	**Vicenzino [28]**
Methods	Design: Repeated measures Randomisation: adequate Blinding: double blind (both patient and assessor) Sample size: Not reported Statistical Analysis: 3 way within subjects analysis of variance
Participants	24 patients Inclusion criteria: unilateral TE of more than 6 weeks. Exclusion criteria: Concomitant conditions, previous manipulative therapy.
Interventions	MWM, placebo and control conditions. 74 sessions in total were administered.
Outcomes	PFG and PPT within side and within subjects.

APPENDIX-4

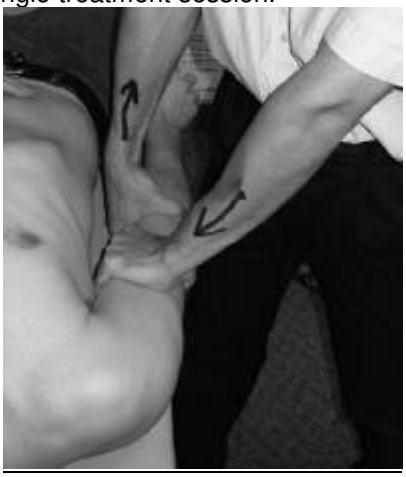
LIST OF ABBREVIATIONS FOR TERMS USED IN APPENDICES 1-3.

Abbreviation	Explanation
LE	Lateral Epicondylalgia
MWM	Mobilization with Movement
CEO	Common Extensor Origin
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CCT	Case Control Study
RCT	Randomized control trial
PGE2	Prostaglandin E2
NK1 r	Neurokinin 1 receptor
ECRB	Extensor Carpi Radialis Brevis
CGRP	Calcitonin related gene peptide
NSAIDs	Non Steroidal Anti Inflammatory Drugs
PFG	Pain Free grip strength
PPT	Pressure Pain Threshold
DOMS	Delayed onset muscle soreness
SNS	Sympathetic Nervous System
VAS	Visual Analogue Scale
MGS	Maximum Grip Strength
UST	Ultrasound Therapy
Rx	Treatment

APPENDIX-5

DESCRIPTION OF LATERAL GLIDE MOBILIZATION WITH MOVEMENT (MWM) FOR LATERAL EPICONDYLALGIA (LE)

MWM are a family of manual therapy techniques with a common theme, which is the application of a joint glide (mobilisation) that is sustained during the performance of an active physical task (movement) by the patient. The physical task in LE is usually a pain free grip measured in units of force by a dynamometer. The treatment technique is performed without any pain and a substantial improvement in grip force is expected during its execution. In the case of a patient with LE of the right elbow, the lateral glide is performed with the patient supine and the affected upper limb fully supported on a treatment table in relaxed elbow extension and forearm pronation (see figure below). The therapist, standing by the patient's right side and facing the patient's head, stabilizes the patient's distal humerus laterally with the heel of his or her left hand and 1st web space. The therapist then applies, from the medial side, a laterally directed glide to the ulna through the 1st web space of his or her right hand. While sustaining the glide, the therapist asks the patient to perform a pain free grip. The change in force with the glide in-situ is noted. It is important to note that ongoing use of this technique is contingent upon a substantial change in pain free grip force during the application of the technique. If successful, the technique may be repeated 6–10 times during a single treatment session.



Figure–2: Mobilization with movement

APPENDIX-6

The levels of evidence outlined by Sackett and his colleagues in 2000 are as follows:

1A = Systematic Review of Randomized Controlled Trials (RCTs)
1B = RCTs with Narrow Confidence Interval
1C = All or None Case Series
2A = Systematic Review Cohort Studies
2B = Cohort Study/Low Quality RCT
2C = Outcomes Research
3A = Systematic Review of Case-Control Studies
3B = Case-control Study
4 = Case Series, Poor Cohort or Case-Control
5 = Expert Opinion