# Hypoalgesia Induced by Elbow Manipulation in Lateral Epicondylalgia Does Not Exhibit Tolerance

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**Abstract: Previous studies have demonstrated that the initial hypoalgesic effect of spinal manipulative therapy was not antagonized by naloxone and did not exhibit tolerance with repeated applications. The implication is that endogenous opioid mechanisms of pain relief are probably not at play in spinal manipulative therapy. The role of endogenous opioid peptides in manipulation of the peripheral joints has not been investigated. The aim of this study was to evaluate whether the initial hypoalgesic effect of a peripheral manipulative technique (mobilization-with-movement treatment for the elbow) demonstrated a tolerance to repeated applications (ie, reduction in magnitude of effect over repeated applications). Twenty-four participants with unilateral chronic lateral epicondylalgia participated in the study. A repeated measures study was conducted to examine the effect of repeated applications of the mobilization-with-movement treatment for the elbow on 6 separate treatment occasions at least 2 days apart. Pain-free grip strength and pressure pain threshold were chosen as the pain-related outcome measures. Changes in the percent maximum possible effect scores of measures of hypoalgesia were evaluated across the 6 treatment sessions by using linear trend analysis. The results showed no significant difference for the hypoalgesic effect of the treatment technique between sessions ($P > .05$). This peripheral manipulative therapy treatment technique appeared to have a similar effect profile to previously studied spinal manipulative therapy techniques, thereby contributing to the body of knowledge that indicates that manipulative therapy most likely induces a predominant non-opioid form of analgesia.**

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***Key words:*** *Endogenous opioid, hypoalgesia, tolerance, pain threshold, manipulative therapy, mobilization-with-movement.*

Since the discovery of endogenous opioid and non-opioid peptides in the late 1970s, a large body of research has evaluated the conditions under which such endogenous pain modulation systems operate. It has been hypothesized that several types of frequently used physical therapies, such as acupuncture, transcutaneous electrical nerve stimulation, vibration, exercise, and manipulative therapy (the skilled treatment application of manual forces to the joint structures), might constitute an adequate input for activating endogenous peptide systems that mediate hypoalgesic effect.[14,17,25,32,41,44] Electroacupuncture is one of the physical treatments that has been extensively investigated, with data showing that differences in stimulation parameters such as frequency[13] markedly influence the endogenous peptide systems. For example, low frequency electroacupuncture (2 Hz) uses $\mu$ and $\delta$ opioid receptors, high frequency (100 Hz) uses $\kappa$ opioid receptors, and 2 to 15 Hz recruits all 3 types of receptors ($\mu$, $\delta$, $\kappa$).[6,7] Interestingly, it has been shown that the hypoalgesic effect produced by electroacupuncture is highly correlated to the effect produced by the same parameters of a transcutaneous electrical nerve stimulation when applied at the same sites.[40] In manipulative therapy there is similar evidence that indicates that different treatment parameters such as frequency profile engender different physiologic effects.[8] Much of the work in manipulative therapy has focused on treatment applied to the spine,[39] predominantly the cervical spine, and our knowledge of treatment applied to the peripheral joints is lacking.

A number of studies on spinal manipulative therapy have indicated that the treatment techniques evaluated bring about pain relief without the apparent involvement of endogenous opioid peptides. The majority of studies that measured plasma $\beta$-endorphin levels from pretreatment to post-treatment have shown that there were no changes with spinal manipulative therapy.[9,24] Testing the presence of an endogenous pain modulation system by measuring plasma levels of the opioid peptides is an indirect method of low sensitivity for determining levels of the peptides within the central nervous system, in which it is likely that they have their mode of operation.[33] Two other widely accepted tests for the identifi-

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cation of endogenous opioid–mediated pain control mechanisms are naloxone antagonism and tolerance.[5,15] Naloxone antagonism involves administration of naloxone to evaluate whether the analgesia is reversed or prevented, whereas the observation of a progressive decline in the magnitude of hypoalgesic effect during a period of repeated treatment applications is how tolerance is identified.[43] Several studies of spinal manipulative therapy have reported that the initial hypoalgesic effect of spinal manipulative therapy is not antagonized by naloxone administration[36,46] and does not exhibit tolerance.[27] It appears that spinal manipulative therapy does not stimulate an endogenous opioid system in bringing about pain relief. It is important to note that this synopsis only relies on the studies of spinal manipulative therapy and that there is a lack of research investigating the effects of manipulative therapy on peripheral joints.

Recent research has shown that a single treatment session of mobilization with movement for the elbow, a peripheral joint manipulative therapy technique, produces substantial and immediate hypoalgesic effect in pain-free grip strength and pressure pain threshold in chronic lateral epicondylalgia.[1,20,21,37,38] The hypoalgesic effect of this technique was not significantly antagonized by naloxone, suggesting a possible involvement of non-opioid form of endogenous analgesia.[22] To further evaluate characteristics of endogenous pain systems and to test the developing theory that manipulation-induced analgesia is a non-opioid–mediated mechanism, we primarily set out to evaluate whether the initial hypoalgesic effect of the mobilization with movement for the elbow (MWME) demonstrated decay over repeated administrations (ie, tolerance).

## Methods

A repeated measures study was conducted to examine the presence of tolerance to repeated applications of the MWME during 6 successive treatment occasions.

### *Participants*

Twenty-four participants (5 women and 19 men) with unilateral lateral epicondylalgia of greater than 6 weeks' duration[37,45] participated in the study. This sample size was shown to be adequate in a previous MWME study, with pain-free grip strength (PFGS) and pressure pain threshold (PPT) as dependent variables.[37] On the basis of this study, 24 subjects were sufficient to detect an effect size (*d*) of 0.73 at $\alpha = .05$ and power of 0.8. Participants were recruited from the Brisbane metropolitan and suburban areas. All volunteers were screened before inclusion into the study by an experienced musculoskeletal physical therapist.

Lateral epicondylalgia was defined as pain over the lateral side of the elbow that was provoked by palpation of the lateral epicondyle region and gripping tasks. In addition, for inclusion into the study pain had to be experienced over the lateral epicondyle during either resisted static contraction or stretching the forearm extensor muscles.[10,35] Participants were excluded from the study if they had cervical spine or other upper limb problems (eg, referred pain). Other exclusion criteria included neurologic impairment, neuromuscular disease, health conditions that would have precluded treatment (eg, osteoporosis, fracture, malignancies, hemophilia), recent steroid injection, use of medications such as analgesic or anti-inflammatory drugs, aversion to manual contact, and previous experience of manipulative therapy to the elbow joint (to minimize expectation bias).[21,22,37] Ethical approval for the study was obtained from the Institutional Review Board (Medical Research Ethics Committee), and all volunteers provided written consent to participate in the study.

**Table 1. Characteristics of the Participants (n = 24) Enrolled in the Study With Data Expressed as Mean ± Standard Error of the Mean**

| | |
|---|---|
| Gender | 5 females, 19 males |
| Age (y) | 49.94 ± 1.46 (range, 33.66–64.75) |
| Duration of condition (mo) | 6.44 ± 0.96 (range, 1.5–18) |
| Right arm dominant | 95.83% |
| Right arm affected | 87.50% |

| | *Affected Arm* | *Unaffected Arm* |
|---|---|---|
| Pain-free grip strength (N) | 122.77 ± 12.03 | 310.19 ± 16.02 |
| Pressure pain threshold (kPa) | 199.17 ± 17.81 | 408.63 ± 29.46 |

Participant details are presented in Table 1. There was an average of 60.42% deficit in PFGS and 51.26% reduction in PPT on the affected side compared to the unaffected side.

### *Outcome Measures*

The measures used to gauge hypoalgesic effect in this study were pain threshold measures consisting of PFGS and PPT. These measures have previously been used in both clinical and laboratory studies of the hypoalgesic effect of physical treatment on lateral epicondylalgia.[1,21,22,26,34-38]

PFGS reflects the degree of impairment associated with lateral epicondylalgia.[10,26,29] It is a measurement of the force required to produce the onset of pain when gripping. PFGS was measured by an electronic digital dynamometer (MIE Medical Research, Leeds, UK) with the participant's arm placed in a standardized position of elbow extension and forearm pronation. The participant was instructed to grip the dynamometer and stop squeezing as soon as pain was first provoked (ie, at pain threshold).[21,22,35,37] Three measures of PFGS were recorded with a 30-second rest interval between each measurement. Intratester reliability of the PFGS measure in this study was considered to be high (intraclass correlation coefficient, 0.97) with a small standard error of measurement (2.37 N).

PPT was measured by using an electronic algometer with a 1-$cm^2$ rubber-tipped transducer (Somedic straingauge type I, Stockholm, Sweden). This measure is somewhat akin to the manual palpation often performed by

practitioners in that it measures the amount of pressure required to cause pain. This was performed by applying the algometer probe tip over the most sensitive point of the lateral epicondyle and applying a pressure at a rate of 40 kPa/s.[21,22,35,37] The test was terminated at the participant's first perception of pain, indicated by a hand-triggered switch.[45] PPT was measured 3 times with a 30-second rest period between each measurement. Intratester reliability for measurements of PPT in this study was acceptable with an intraclass correlation coefficient of 0.95 and a standard error of measurement of 5.92 kPa.

## MWME Treatment Technique

The MWME treatment technique involved the application of a lateral glide mobilization with movement for the elbow as described by Mulligan.[20] The participant was in a supine position with the upper limb in the following position: shoulder internal rotation, elbow extension, and forearm pronation.[21,22,37,38] To apply this technique, the therapist used one hand to stabilize the distal humerus on the lateral side and the other hand to apply to the medial side of the proximal forearm a laterally directed glide to the ulna and radius. The glide was painlessly applied and sustained while the participant performed a pain-free gripping action. The glide was maintained until the participant completely released the grip. The procedure takes approximately 6 seconds to perform. Ten repetitions of the treatment technique were performed with an approximate 15-second rest interval between repetitions.[38] The MWME technique applied in this study was consistent with those applied in other studies of lateral epicondylalgia.[21,22,37,38]

## Experimental Procedures

A preliminary session was conducted to confirm diagnosis of lateral epicondylalgia and to screen participants for inclusion and exclusion criteria. Suitable participants were familiarized with the laboratory environment, laboratory staff, testing procedures, and layout of experimental session.

Each participant attended the laboratory on 6 occasions with approximately 48-hour interval between sessions.[16] They attended at a similar time each day to assist in controlling any influence of diurnal variation on the outcome measures. During each of the 6 sessions the participant received an identical MWME treatment technique. In all of the study, 144 experimental sessions were undertaken (ie, 24 participants $\times$ 6 sessions). The study was conducted in an environment-controlled laboratory (constant temperature, humidity, and noise attenuation). All participants were requested to avoid factors that might interfere with the pain outcome measures such as consuming stimulants (eg, caffeine and nicotine product) or taking analgesic drugs for at least 6 hours before the experimental session[30] and heavy exercise about 4 hours before the session.[14] The participants were also requested not to change their usual sleep patterns. Adherence to these requirements was evaluated by way of questionnaires completed before each experimental session, and if a lapse had occurred, the participant was rescheduled for another time. No participant was rescheduled on this basis in the study.

At each experimental session the participant was positioned in a supine position on a therapeutic plinth. Pretreatment measurements of PFGS and PPT were taken on both unaffected and affected sides, followed by application of the MWME treatment technique to the affected arm. During application of the treatment technique, the PFGS was also measured on the affected (treated) side. The pain outcome measures (ie, PFGS, PPT) were again evaluated immediately after treatment application. A different investigator to the one applying the MWME treatment technique measured all outcome measures and was unaware of the treatment being applied. The participant and therapist applying the treatment were blinded to the outcome.

## Data Management and Analysis

To evaluate the primary question being addressed by this study, the triplicate data of PFGS and PPT were averaged and expressed as a percentage of maximum possible effect (MPE) according to the formula: MPE = 100 $\times$ [Post-treatment score$_{(\text{affected side})}$ $-$ Pretreatment score$_{(\text{affected side})}$] $\div$ [Pretreatment score$_{(\text{unaffected side})}$ $-$ Pretreatment score$_{(\text{affected side})}$]. This method of analysis (MPE) has been used in previous tolerance studies to determine tolerance characteristic for antinociceptive effect of certain physical stimulation and pharmacologic administration.[16,23] Changes in MPE of the hypoalgesic effect across the 6 treatment sessions were then evaluated by using linear trend analysis with statistical significance being determined at the $\alpha$ level of 0.05 ($P \leq .05$).[18] The data were analyzed with the SPSS statistical package, version 11.0 (SPSS Inc, Chicago, Ill).

A secondary issue resulting from the administration of a manipulative therapy treatment technique like the MWME is that, in a clinical context, administration of the treatment technique repeatedly during several treatment sessions is expected to result in an improvement in the client's condition.[20,38] To evaluate this clinical expectation, the preapplication baseline data normalized to the unaffected side[4] ([Score of affected side $\div$ Score of unaffected side] $\times$ 100) between the 6 days on which the treatment was administered was analyzed with a 1-way repeated measures analysis of variance with days (1, 2, 3, 4, 5 or 6) as the factor.

# Results

All 24 participants completed the study, and there were no adverse effects or complications reported during or after the experimental sessions.

## Tolerance Aspect of Study

The MWME treatment technique produced a hypoalgesic effect with a mean MPE ($\pm$ standard error of mean [SEM]) of 38.84% ($\pm$7.05%) in PFGS during the technique's application, 45.29% ($\pm$8.12%) in PFGS immediately after treatment application, and 17.51% ($\pm$6.95%)

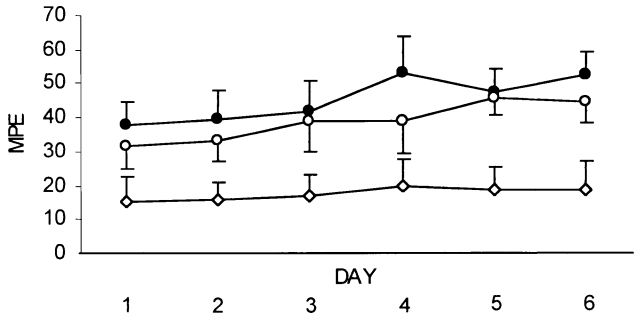


**Figure 1.** The mean ± SEM hypoalgesic effect expressed as MPE scores in PFGS during (open circle) and after (closed circle) application and PPT (open diamond) during 6 successive sessions.

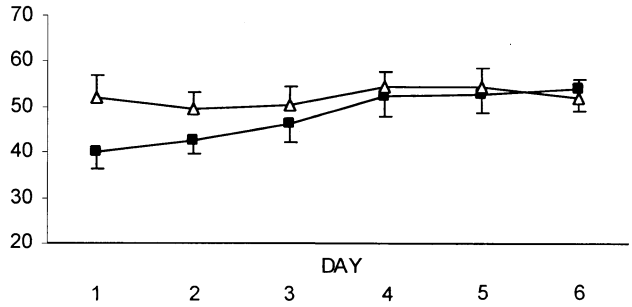


**Figure 2.** Mean percentage scores (± SEM) of the normalized-baseline values (affected side/unaffected side) for PFGS (closed square) and PPT (open triangle) during 6 successive sessions.

in PPT across all experimental sessions (Fig 1). There were no significant differences demonstrated between sessions ($P > .05$) for the hypoalgesic effect as measured by MPE (Table 2). No tolerance appeared to develop in the initial hypoalgesic effect of the MWME.

Instead of a reduction in effect of the MWME on the PFGS measure, there was a trend for an increase in MPE during the course of repeated administrations. Linear trend analysis with a time factor (days) as a covariant was performed to examine the significance and magnitude of these changes. The results showed a significant increase in magnitude of PFGS during treatment application of approximately 2.96% for each session ($F = 5.23$; $df = 1, 119$; $P = .02$). PFGS after the technique application also increased 3.06% per session ($F = 3.85$; $df = 1, 119$; $P = .05$). Data did not support a similar increase in PPT across observation periods ($F = 0.29$; $df = 1, 119$; $P = .59$).

### *Anticipated Improvement With Repeated Applications During Sessions*

Improvement in PFGS but not PPT data collected before treatment application on the 6 days was observed (Fig 2). Statistical analysis concurred with these observations, with PFGS data being significantly different on days 4, 5, and 6 when compared to baseline values on day 1 ($P < .01$, Table 3). The magnitude of improvement from day 1 to day 6 was in the order of 35.4%. There was no significant main effect for days on the PPT data ($F = 0.70$; $df = 5, 115$; $P = .62$).

## Discussion

The hypoalgesic effect of MWME on PFGS and PPT did not reduce with repeated applications of the treatment technique during 6 successive sessions (Fig 1). Instead, the PFGS increased significantly with repeated applications, most notably seen with baseline measures on days 4 through 6 (Fig 2). The hypoalgesic effect in these pain measures did not become tolerant to the repeated application of the treatment. The lack of reduction in effect in PFGS and PPT during repeated applications of MWME implies that opioid peptides do not appear to play a significant role in the initial pain-relieving effects of the studied peripheral joint manipulation treatment technique. In so far as tolerance and naloxone antagonism[5,15] are deemed sufficient properties of an endogenous opioid–mediated pain suppression system, this finding is in agreement with a previous study that showed the MWME-induced hypoalgesia was not antagonized by naloxone.[22] It would appear from the findings of this study and others[9,22,24,27,28,34,36,46] that it is unlikely that endogenous opioid–mediated pain inhibitory systems play a substantial role in a range of manipulative therapy treatments of the spinal or peripheral joints.

This study confirmed that the MWME treatment technique is capable of producing hypoalgesic effects during and after its application, as demonstrated by improvement in PFGS during treatment (approximately 38.8%)

**Table 2. Results of Linear Trend Analysis Across Experimental Sessions for the Hypoalgesic Effect of Pain Outcomes (n = 24)**

| Outcome Measures | F Value ($df = 5,115$) | P Value |
|---|---|---|
| Pain-free grip strength (during application) | 1.10 | .37 |
| Pain-free grip strength (after application) | 0.98 | .44 |
| Pressure pain threshold | 0.08 | .99 |

**Table 3. Results of an Omnibus One-Way Repeated Measures Analysis of Variance and A Priori Contrasts for the Normalized Baseline Data (n = 24)**

| Analysis | F Value | df | P Value |
|---|---|---|---|
| 1-Way analysis of variance | 5.93 | 5, 115 | <.001 |
| Specified contrasts | | | |
| Day 1 vs day 2 | 0.71 | 1, 23 | .41 |
| Day 1 vs day 3 | 3.23 | 1, 23 | .09 |
| Day 1 vs day 4 | 9.69 | 1, 23 | <.01 |
| Day 1 vs day 5 | 8.58 | 1, 23 | <.01 |
| Day 1 vs day 6 | 9.06 | 1, 23 | <.01 |

and immediately after treatment (45.3%). There was a 17.5% improvement in PPT immediately after treatment. This pattern of initial hypoalgesic effect is supported by findings in previous studies in which the MWME treatment produced an immediate improvement in PFGS (37% to 58%), which was of greater magnitude than a cervical spine manipulative treatment technique (12% to 30%) for lateral epicondylalgia.[21,34,35,37] Interestingly, the increase in PPT (10% to 15.4%) was less than for spinal manipulative therapy (25% to 30%).[21,34,35,37] These differences in effect on PFGS and PPT between peripheral and spinal treatments might be due to the different body regions being manipulated[12] and the difference in frequency profile of the techniques,[8] in this way paralleling findings from acupuncture studies that showed the acupuncture-induced analgesic effect was dependent on the treated body region and the frequency of stimulation.[11,13]

The trend for the hypoalgesic effect as measured by changes in PFGS was for it to increase over time from the first session to the sixth session. It is plausible that the increase in outcome measures was due to the natural history of the condition or placebo effects; however, these factors seem unlikely to be the major contributors for several reasons. First, the hypoalgesic effect was evaluated from pretreatment to post-treatment for each session, indicating that it was induced by treatment administration rather than by time between sessions. In addition, a number of studies[1,21,37] have found that the MWME technique was able to produce an immediate hypoalgesic effect after treatment application that was greater than placebo.[21,37] Second, the trend of increase in hypoalgesic effect was demonstrated in PFGS, but not in PPT. If spontaneous recovery, natural resolution, or placebo effects were mainly responsible for the improvement, we would plausibly expect these trends in both PFGS and PPT.

Resistance to the development of tolerance after repeated treatment applications makes the MWME treatment technique a treatment approach that would appear useful during a course of treatment for lateral epicondylalgia. The main aim of this study was not to determine the clinical efficacy of the treatment technique to improve function or reduce disability; however, analysis of the effect of repeated applications on the baseline data for each treatment session showed that the PFGS measure, but not PPT, was significantly improved after the repeated sessions. A randomized control trial of this treatment technique is now required to properly address the efficacy of this treatment technique during a course of treatment in a clinic.

The neural system responsible for manipulative therapy–induced pain modulation is likely complex. Previous studies have suggested that manipulative therapy might provide an adequate non-noxious sensory input to activate descending pain inhibitory system (DPIS) as a major component of its pain-relieving effects.[28,34,35,42] Studies on animals have demonstrated that the midbrain periaqueductal gray plays a pivotal role in DPISs.[2,3] Research in animal models has shown that stimulation of the midbrain periaqueductal gray at the sites that use opioid peptides produces opioid analgesia as demonstrated by tolerance that occurs with as little as 3 successive sessions of 60-second stimulus duration with 48-hour rest intervals between sessions.[16] In contrast, stimulation on the sites of the lateral-dorsal periaqueductal gray demonstrates a non-opioid form of analgesia that is not tolerant to repeated applications[19,31] and is insensitive to a naloxone blockade.[5] In addition, stimulation of this lateral-dorsal periaqueductal gray area appears to result in a rapid hypoalgesia accompanied with sympathoexcitation.[2,3] Manipulative therapy studies showed that both the spinal[28,34] and peripheral (MWME)[21] treatment techniques produced immediate and concurrent changes in hypoalgesia with sympathetic activation. Moreover, the hypoalgesic effect of manipulative therapy was unaffected by naloxone and did not develop tolerance,[22,27,36,46] paralleling the feature of a DPIS initiated by stimulation of the lateral-dorsal periaqueductal gray.[2,3]

## Conclusion

The peripheral manipulative therapy treatment technique evaluated in this study appears not to become tolerant to repeated administrations, with possible implications on the mechanisms of action of manipulative therapy.

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