

NALOXONE FAILS TO ANTAGONIZE INITIAL HYPOALGESIC EFFECT OF A MANUAL THERAPY TREATMENT FOR LATERAL EPICONDYLALGIA

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ABSTRACT

Background: Recent research has shown that Mulligan's Mobilization With Movement treatment technique for the elbow (MWM), a peripheral joint mobilization technique, produces a substantial and immediate pain relief in chronic lateral epicondylalgia (48% increase in pain-free grip strength).¹ This hypoalgesic effect is far greater than that previously reported with spinal manual therapy treatments, prompting speculation that peripheral manual therapy treatments may differ in mechanism of action to spinal manual therapy techniques. Naloxone antagonism and tolerance studies, which employ widely accepted tests for the identification of endogenous opioid-mediated pain control mechanisms, have shown that spinal manual therapy-induced hypoalgesia does not involve an opioid mechanism.

Objective: The aim of this study was to evaluate the effect of naloxone administration on the hypoalgesic effect of MWM.

Methods: A randomized, controlled trial evaluated the effect of administering naloxone, saline, or no-substance control injection on the MWM-induced hypoalgesia in 18 participants with lateral epicondylalgia. Pain-free grip strength, pressure pain threshold, thermal pain threshold, and upper limb neural tissue provocation test 2b were the outcome measures.

Results: The results demonstrated that the initial hypoalgesic effect of the MWM was not antagonized by naloxone, suggesting a nonopioid mechanism of action.

Conclusions: The studied peripheral mobilization treatment technique appears to have a similar effect profile to previously studied spinal manual therapy techniques, suggesting a nonopioid-mediated hypoalgesia following manual therapy. (*J Manipulative Physiol Ther* 2004;27:180-5)

Key Indexing Terms: *Endogenous Opioid; Hypoalgesia; Manual Therapy; Mulligan's Mobilization; Naloxone; Pain Threshold*

INTRODUCTION

A number of systemic reviews have shown that manual therapy, the skilled application of manual forces to the joint structures, provides effective results in treatment of musculoskeletal pain.²⁻⁴ Much of the research of the neurophysiological effects of

manual therapy has focused on spinal techniques and has implicated that mobilization-induced hypoalgesia does not involve endogenous opioid mechanisms.^{5,6} This evidence arises from studies that have shown that manual therapy-induced hypoalgesia is not antagonized by naloxone,^{7,8} fails to develop tolerance,⁹ and occurs in the presence of normal plasma endorphin levels.^{10,11} In addition to these findings, several studies of spinal manual therapy have indicated the specificity for techniques to produce mechanical but not thermal hypoalgesia,^{6,12,13} implicating endogenous noradrenergic rather than serotonergic mechanisms.¹⁴

Mulligan's Mobilization With Movement (MWM) has been shown to exert a substantial and rapid pain-relieving effect in patients with chronic lateral epicondylalgia.^{1,15,16} It is a recently developed manual therapy treatment technique that involves the application of a sustained glide and active movement across a peripheral joint.¹⁷ The role of endogenous opioid peptides in MWM-induced

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hypoalgesia has not been investigated and is the aim of this study. This study utilized a widely accepted test of endogenous opioid mechanisms, naloxone antagonism, to evaluate the role of such mechanisms in MWM-induced hypoalgesia.

METHODS

This study utilized a randomized, placebo-controlled, crossover, double-blind, repeated measures design to evaluate the hypothesis that MWM-induced hypoalgesia was antagonized by naloxone.

Participants

Eighteen participants with unilateral chronic lateral epicondylalgia participated in the experiment. A previous naloxone study in manual therapy showed this was an adequate sample size.⁷ All volunteers were screened before inclusion into the study by an experienced postgraduate trainee in orthopedics. Chronic lateral epicondylalgia was diagnosed clinically as pain over the lateral side of the elbow, which was provoked by digital palpation of the lateral epicondyle and gripping tasks.¹⁸ Inclusion and exclusion criteria have been described in previous studies.^{1,13} For the safety concern of using naloxone, the additional exclusion criteria included cardiovascular disease, pulmonary disease, liver disease, renal failure, drug addiction, and pregnant and breastfeeding women.¹⁹

Participant demographics are presented in Table 1. There was a 48% deficit in pain-free grip strength on the affected side compared with the unaffected side, 40% reduction in pressure pain threshold, 34% reduction in upper limb neural tissue provocation test 2b, and 5% reduction in thermal pain threshold. All participants gave informed consent in written form prior to participation, and the Institutional Review Board for research in humans granted ethical clearance for this study.

Outcome Measures (Dependent Variables)

Pain threshold values during the various tests (pain-free grip strength, pressure pain threshold, thermal pain threshold, upper limb neural tissue provocation test 2b) were assessed as the pain outcome measures. All these measures have previously been used in the laboratory.^{1,6,7,12,13}

Pain-free grip strength. Pain-free grip strength (PFGS) is the amount of grip force required to produce the first onset of pain (ie, pain threshold).²⁰ It 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 by the participants' side. 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 high

Table 1. Characteristics of the 18 study participants enrolled into the study at the start of the project

Gender	4 female, 14 male	
Age	48.67 ± 2.38 (range, 24-65.25 years)	
Duration of condition	9.74 ± 1.82 (range, 1.75-24 months)	
Right arm dominant	94.44%	
Right arm affected	77.78%	
	Affected arm	Unaffected arm
Pain-free grip strength (N)	139.37 ± 17.12	268.10 ± 16.55
Pressure pain threshold (kPa)	279.60 ± 28.57	466.98 ± 29.37
Thermal pain threshold (°C)	44.40 ± 0.61	46.92 ± 0.54
Neural tissue provocation test 2b (°)	9.83 ± 1.31	15.11 ± 2.31

Continuous data expressed as mean ± standard error of the mean.

(ICC = 0.98) with a small standard error of measurement (SEM_{Meas} = 1.72 N).

Pressure pain threshold. A digital algometer with a 1 cm² rubber tipped transducer (strain-gauge type I, Somedic, Stockholm, Sweden) was used to measure pressure pain threshold (PPT) over the most tender point of the lateral epicondyle, with pressure application rate of 40 kPa/sec.¹³ Pressure pain threshold was measured 3 times with approximately 30-second rest interval between each measurement. The intratester reliability for PPT in this study was considered to be high, with an ICC of 0.96 and a SEM_{Meas} of 5.66 kPa.

Thermal pain threshold. Thermal pain threshold (TPT) over the lateral epicondyle was measured using a contact thermode system (Somedic AB, Frestavagen, Sweden). The participant signaled the pain onset (when the heat sensation first became one of heat and pain) by pressing a hand-controlled switch.¹² Thermal pain threshold was measured 3 times, and the analogue signals of TPT were collected on an IBM-compatible personal computer. Intratester reliability of TPT in this study was high, with an ICC of 0.94 and a SEM_{Meas} of 0.21°C.

Upper limb neural tissue provocation test 2b. The upper limb neural tissue provocation test 2b (ULTT2b) was used to assess the nociceptive withdrawal reflex of the upper limb with a bias toward the radial nerve. It was carried out using the procedures described by Yaxley and Jull.²¹ The shoulder was then abducted by the examiner to the first onset of pain,¹³ again indicated by a hand-triggered switch. The angle of shoulder abduction was measured 2 times by an electrogoniometer (Penny & Giles, Blackwood Gwent, UK); the analogue signal from the electrogoniometer was obtained on a National Instrument AD card (National Instruments, Austin, Texas). Intratester reliability of ULTT2b

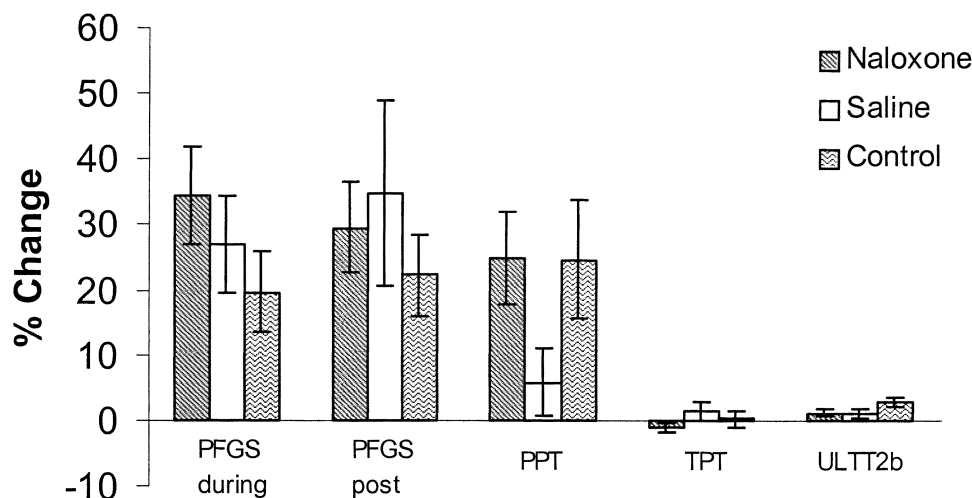


Fig 1. The mean \pm SEM hypoalgesic effect expressed as percentage changes in pain-free grip strength (during and post-PFGS), pressure pain threshold (PPT), thermal pain threshold (TPT), and upper limb neural tissue provocation test 2b (ULTT2b) under the naloxone, saline, and control conditions.

in this study was considered to be high, with an ICC of 0.98 and a SEMeas of 0.20° .

Experimental Conditions

Intravenous administration of naloxone and normal saline along with a no-substance control condition were the experimental conditions used in this study. Naloxone was injected as naloxone hydrochloride 0.8 mg in 2 mL by means of a 22-gauge intravenous cannula into the unaffected side over a period of 30 seconds. The cannula insertion was performed under cutaneous anesthesia (0.2 mL of 2% lidocaine). The placebo condition consisted of 2 mL normal saline administered as per the naloxone procedure. The control condition involved the insertion of cannula by the same manner as in the naloxone procedure but without any naloxone or saline solution. Intravenous administration of either the naloxone, saline, or control conditions was applied under the injection sheet (to obtain the subject blinding status). A general medical practitioner, who played no role in data collection/analysis, administered these conditions for each participant in a concealed randomized order over the 3 separate days. The experimental condition that each participant experienced on any one day was achieved by randomization through the rolling of a dice. This randomization process resulted in 5 participants receiving the naloxone condition on Day 1 (D1), another 5 participants receiving it on Day 2 (D2), and the remaining 8 participants receiving it on Day 3 (D3).

MWM Treatment Technique

Typically, on each day, each participant received the MWM treatment technique soon after the administration of the experimental condition (ie, naloxone, saline, or

control). The MWM technique performed in this study is consistent with those applied in previous studies.^{1,16,17} An experienced therapist used one hand to stabilize the distal end of the humerus on the lateral side just proximal to the elbow joint, while the other hand applied a laterally directed glide of the proximal ulnar and radius. The glide was painlessly applied and sustained while the participant performed the pain-free gripping action. Six repetitions were applied with approximately 15-second rest intervals between repetitions.

Experimental Procedure

A preliminary session was conducted to screen participants for inclusion into the study. It also served to provide instructions and familiarize participants with the laboratory environment, testing procedures, and laboratory staff. To minimize possible carryover effects and effects due to diurnal variation, each participant attended the 3 experimental sessions at about the same time of the day on 3 different days, with at least 48 hours between sessions. At each session, the participant experienced one of the experimental conditions (ie, naloxone, saline, or control) in a predetermined randomized order. The study was conducted in an environment controlled laboratory (noise attenuated, average temperature $23.2^\circ\text{C} \pm 0.5^\circ\text{C}$, and relative humidity $61.4\% \pm 5.35\%$). There was no significant difference in room temperature ($F_{2,34} = 2.01$, $P = .15$) and relative humidity ($F_{2,34} = 1.07$, $P = .35$) between the 3 experimental conditions.

All participants were requested to avoid factors that may interfere with the pain outcome measures, such as consuming stimulants (eg, caffeine and nicotine products) or taking analgesic drugs for at least 6 hours prior to the study¹⁹ and heavy exercise about 4 hours before the study.²² Participant

compliance was assessed by means of a pre-session questionnaire administered prior to each experimental session, and if a lapse had occurred, the participant was then rescheduled for another time.

After completion of the pre-session questionnaire, the participant was positioned in the supine position on a therapeutic plinth. The scores of pain threshold measurements (PFGS, PPT, TPT, ULTT2b) were first taken before either the naloxone, saline, or control conditions were applied. Immediately after the administration of the experimental conditions, an experienced therapist applied the MWM for the elbow on the affected side. The PFGS was also measured during the technique application. The pain outcome measures (PFGS, PPT, TPT, ULTT2b) were then repeated again immediately after the application of the treatment technique.

The therapist and the investigator, who was responsible for outcome measurement, remained blind to whether naloxone, saline, or control had been administered. The participants were also blind to the condition applied on each experimental session. Postexperimental questionnaires revealed that no participants were able to identify the specific conditions which were applied during the experimental session. This information supported that the participant blinding status was maintained.

A potential limitation of a crossover design is that there may be a carryover effect or an order effect as a result of a participant receiving all 3 conditions. A carryover effect is where the effect of an experimental condition experienced at a preceding session is still present at later study sessions, such that the preapplication baseline data is different between study days (ie, baseline levels between study days are not equal). An order effect is when a response to an experimental condition differs on different study days (D1, D2, D3). For example, an order effect would be present if the naloxone effect was different on Day 3 (D3) to that of Day 1 (D1). Several methodological features were used in this study to account for possible carryover and order effects of the crossover design, such as randomization of experimental conditions, maintaining an interval of at least 48 hours between experimental sessions, and statistically evaluating the data for these possible experimental procedure-related effects. Carryover effects on baseline data were evaluated with a 1-way analysis of variance (ANOVA) with the factor being days (D1, D2, or D3). The preapplication data for primary outcome measures were not different among experimental session days (PPT: $F_{2,34} = .55$, $P = .58$, PFGS: $F_{2,34} = 3.02$, $P = .06$). Order effects were analyzed by a 1-way ANOVA of the change score for naloxone, the experimental condition of interest, between days (D1, D2, D3). There was no significant difference in the naloxone effect between days (PPT: $F_{2,15} = .43$, $P = .66$, PFGS: $F_{2,15} = .82$, $P = .46$). These results indicate that the carryover or order effects, which could be attributed to the experimental procedure (ie,

Table 2. One-way within-subjects ANOVA results (three levels of conditions: naloxone, saline, and control) for pain outcomes

Dependent variable (n = 18)	$F_{2,34}$	P-value
Pain-free grip strength (during)	1.54	.23
Pain-free grip strength (post)	0.54	.59
Pressure pain threshold	2.75	.08
Thermal pain threshold	0.91	.41
Neural tissue provocation test 2b	1.56	.22

ANOVA, Analysis of variance.

within-subjects and crossover design), did not influence the outcome of the study.

Data Management and Analysis

The data was analyzed using SPSS statistical package (version 11.0, SPSS, Chicago, Ill). The triplicate data of PFGS, PPT, and TPT and the replicate data of ULTT2b were averaged and then expressed as a percentage change from preapplication to postapplication data. This served to subsume variation effects between participants and allow direct comparisons in effect across all variables, as well as across the studies, which have used the same method of analysis.^{1,6,7,12,13,23-26}

This study investigated the influence of intravenous naloxone on the MWM-induced hypoalgesia. The specific effect of naloxone was evaluated in comparison with the placebo and control conditions. Statistical comparisons among conditions were performed using a 1-way within-subjects analysis of variance. Statistical significance was determined at the alpha-level of .05.

RESULTS

The MWM treatment technique produced a mean hypoalgesic effect of 29% (± 5.6 , SEM) in PFGS, 18% (± 4.3) in PPT, 1.6% (± 0.4) in ULTT2b, and 0.2% (± 0.7) in TPT across all experimental conditions. Figure 1 shows the percentage changes of pain outcomes for each of the experimental conditions (naloxone, saline, control). There was no statistical difference between naloxone, saline, or control conditions (Table 2).

All 18 participants completed the study, and there were no adverse effects or complications reported.

DISCUSSION

The findings of this study showed that naloxone did not significantly antagonize the initial hypoalgesic effect of the MWM for the elbow when compared with a placebo saline injection or no-substance injection control. This result is similar to that of Zusman et al⁸ and Vicenzino et al,⁷ who found no effect of naloxone on spinal manual

therapy-induced hypoalgesia, suggesting that the manual therapy may mainly induce a nonopioid form of analgesia as part of its effect.^{5,7,8}

The initial MWM-induced hypoalgesia appears to be expressed primarily in the functional pain threshold test of PFGS and to a lesser extent by the PPT measure of hypoalgesia but not TPT. These findings corroborate with previous research confirming selective mechanical hypoalgesia with manual therapy.^{1,6,13} The failure of naloxone to antagonize the hypoalgesic effect of peripheral manual therapy implicates the involvement of nonopioid and possibly noradrenergic endogenous pain modulation mechanism(s).¹⁴

Failure of naloxone to antagonize MWM hypoalgesia in itself is not the final or definitive test of opioid system involvement in this physical treatment. Naloxone predominantly binds with the mu-receptor, which is only one receptor subtype through which an opioid-related analgesic response could be mediated.²⁷ Other endogenous opioid peptides could possibly be involved in MWM-induced hypoalgesia and they would not be antagonized or only partly antagonized by naloxone. Other tests for determining endogenous opioid-mediated pain modulation mechanism, such as determining tolerance to the treatment-induced hypoalgesic effect,⁹ are currently being undertaken in our laboratory.

Factors that may have contributed to a lack of naloxone antagonism are the dose used and the half-life of naloxone. The 0.8-mg dose of naloxone hydrochloride used in this study has been shown to be sufficient to reverse or partially block the hypoalgesic effect of therapeutic interventions, such as acupuncture and transcutaneous electrical stimulation (TENS).²⁸⁻³¹ This dose was also the highest dose considered ethically safe to administer in this experimental circumstance.³² The half-life of naloxone of 60 minutes far exceeded the time taken to apply the treatment technique and retake the outcome measures.¹⁹ In addition, the treatment technique in this study was applied within a time frame that was close to the dominant pharmacological effect period of 1 to 2 minutes postadministration of naloxone.^{19,33} We are therefore confident that should a naloxone reversible hypoalgesia be present following MWM, that we would have observed it. A position that we feel is somewhat confirmed by the results of a power analysis of the naloxone effect on the MWM-induced hypoalgesia in which it was determined is that for such a small effect size (effect size index $[d]=0.12$), an unrealistic number of subjects (in the order of 1100 subjects for PFGS) would need to be studied.^{34,35} That is, the likelihood of a type II error being present as a result of an insufficient sample size is remote.

CONCLUSION

The initial hypoalgesic effect produced by the MWM for the elbow was not significantly antagonized by pretreatment intravenous injection of naloxone, supporting the hypothesis

that manual therapy-induced hypoalgesia most likely involves a nonopioid mechanism of action.

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