**Introduction**

The proposed research is part of a PhD project that will evaluate the analgesic responses induced by two specific forms of endogenous analgesia: manual therapy induced pain modulation (MIPM) and conditioned pain modulation (CPM). To achieve this, three main experimental studies will assess the analgesic responses produced by both paradigms using three different experimental interventions, namely: physiotherapeutic, psychological, and pharmacological interventions. This will eventually help determine if both paradigms share similar neurophysiological mechanisms.

In this proposed experimental study, CPM and manual therapy analgesic responses will be assessed using CPM and MIPM assessment protocols, respectively, in patients with Lateral Epicondylalgia (LE). Participants will initially undergo a through clinical screening to confirm that eligibility criteria are met. Eligible participants will then undergo CPM assessment followed by MIPM assessment, with a 15mins rest in between (subject to findings from Pilot Study: HRE2016-0181).

Both protocols will use pressure pain threshold (PPT) as the main outcome measure to quantify the analgesic changes in response to the proposed experimental interventions. The PPT values will then be analysed to determine if there is an association between the CPM and MIPM responses in this patient population. If both forms of pain modulation demonstrate a similar pattern of response, this would suggest a common underlying mechanism of action. It is also expected that a proportion of subjects will demonstrate no CPM effect (CPM non-responders). This will be determined through calculation of meaningful CPM effect using the criterion described by Locke et al. (2014) to determine meaningful CPM effect. MIPM measures will be used to compare the MIPM effect between those who exhibit a CPM effect (CPM responders) and those who do not demonstrate a CPM effect (CPM non-responders).

This research may provide a base from which to investigate the possibility of enhancing MIPM effects by combining manual therapy with other treatment modalities. It will therefore extend our knowledge of manual therapy induced analgesia.

**Study One: *Association between the analgesic effects of CPM and MIPM***

**Aims**

* To assess CPM and MIPM in a patient population with Lateral Epicondylalgia (LE) to determine if there is a correlation between the induced analgesic responses in this patient population.
* To determine whether there is a difference in the level of MIPM analgesia between those who exhibit a CPM effect (CPM responders) and those who do not demonstrate a CPM effect (CPM non-responders).

**Null hypotheses**

1. There will be no correlation between the level of MIPM and CPM analgesia as detected by PPT.
2. There will be no difference in the level of MIPM analgesia between those subjects who do and those who do not exhibit a CPM effect (CPM responders vs non-responders).

**Methods**

**Subjects**

Participants with LE will be recruited through Curtin radio advertisements, and adverts in sports clubs and a range of musculoskeletal and sports physiotherapy clinics in Perth. Using data from previous CPM studies, it is estimated that there would be a difference in percentage change in PPT of approximately 20% between active intervention and control groups. Assuming power of 0.80 and alpha set at 0.05, this would require 26-30 subjects per group. Inclusion criteria (Haker & Lundeberg 1990) and exclusion criteria are as follows:

***Inclusion criteria***

|  |
| --- |
| Unilateral elbow pain > 6 weeks reproduced on **at least 2** of the following tests:  |
| Palpation of the lateral epicondyle | Passive stretch of wrist extensors |
| Isometric testing of the wrist extensors | Resisted hand gripping using a dynamometer |
| Middle finger extension test | Upper limb neurodynamic test-radial nerve bias |

***Exclusion criteria***

|  |  |
| --- | --- |
| Neurological and radicular dysfunctions | Steroid injection into the elbow (previous 1 month)  |
| History of fracture/surgery in the forequarter (past 2 y) | Contraindications to cold applicationInability to communicate in English |
| History of generalized arthritis |  |
| Present or chronic use of anti-depressants |  |

To confirm that the eligibility criteria are met, a thorough clinical examination of all subjects will be carried out prior to commencing the study. Subjects will also be required to initially complete Adult Pre-exercise Screening System (APSS) tool, which is an Australian screening tool developed by Exercise and Sport Science Australia (ESSA), Fitness Australia (FA), and Sports Medicine Australia (SMA) to examine participants’ eligibility and safety for aerobic exercise testing (Norton & Norton 2011). All testing will be carried out at the Physiotherapy Clinic, School of Physiotherapy and Exercise Science, Curtin University. Subjects will be asked to avoid taking pain medications 24 hours prior to initial testing.

**Physical activity level outcome measure**

All eligible participants need to report their typical week physical activity level using the Global Physical Activity Questionnaire (GPAQ) (WHO 2005). It is a 16-questions self-reported questionnaires measuring physical activity levels in three main areas: work, transport and recreation. The GPAQ is shown to be an adequately reliable measure of physical activity, with a low-to-moderate validity (Herrmann et al. 2013).

**Pain-related outcome measures**

**Pressure pain threshold (PPT)**

PPT will be measured using an electronic digital algometer (Somedic AB, Sweden) with standard methodology ([Coombes](http://www.ncbi.nlm.nih.gov/pubmed/?term=Coombes%20BK%5BAuthor%5D&cauthor=true&cauthor_uid=24480912) et al. 2015). PPT is a highly reliable measure for assessment of pain in LE (ICC > 0.86) (Fernández-Carnero et al. 2009). The assessor will identify the most tender point at the lateral aspect of the affected elbow by palpation. He will also identify a mid-point on the posterior aspect of the wrist, 2 cm proximal to the wrist crease. These measurement sites will then be marked. The participant will be sitting on a chair of adjustable height so the forearm is comfortably positioned in pronation on a table. A 1 cm² algometer tip will be applied perpendicularly over each marked site by the assessor and the pressure stimulus applied at a standard rate of 40 kPa/s. The participant will be instructed to push a control switch at the moment they perceive the pressure becoming painful. PPT measures are the pressure value (kPa) recorded from the algometer. The test procedure will first be conducted at the unaffected forearm for familiarization. Three PPT measurements will be taken at each site on the symptomatic side with 10-15 s intervals between each. Mean values will be used in analysis.

**Pain free grip (PFG)**

Pain on gripping is a clinical sign of LE (Vicenzino et al. 1998). Pain free grip (PFG) refers to the amount of grip force that can be applied prior to the onset of pain (Paungmali et al. 2003). PFG will be measured with an electronic digital dynamometer (MIE, Medical Research Ltd.) using standard methodology ([Coombes](http://www.ncbi.nlm.nih.gov/pubmed/?term=Coombes%20BK%5BAuthor%5D&cauthor=true&cauthor_uid=24480912) et al. 2015). It is both a reliable (ICC > 0.97) (Smidt et al. 2002) and valid (Paungmali et al. 2003) measure used in patients with LE. The participant will be lying supine with the arm by their side positioned in elbow extension and forearm pronation. They will then be requested to squeeze the dynamometer handles until they first feel their lateral elbow pain, and then to stop the squeezing action. The PFG force value is then recorded from the digital display. The PFG test will be performed three times with 10-20 s rest intervals in between. The average value will then be used for analysis.

**Upper limb neurodynamic test (ULNDT) with radial nerve bias**

The upper limb neurodynamic test (ULNDT) with radial nerve bias will be used to assess primarily neural mobility of the forequarter (Butler 2000). Painfree range of motion in the test is restricted in patients with LE (Yaxley & Jull 1993). The participant’s arm will be progressively positioned in scapular depression and protraction, elbow extension, internal rotation, forearm pronation, wrist and finger flexion. Scapular depression will be sustained while performing the test. The shoulder will then be slowly taken into abduction. The participant will be instructed to depress a switch at the onset of pain with this movement and the arm will be returned to the start position. The shoulder abduction range at the onset of pain will be measured using an M180 twin axis electrogoniometer (Penny & Giles, United Kingdom) positioned over the anterior shoulder (Vicenzino et al. 1996). Three readings will be taken with 20-30 s intervals in between. The average of these readings will be used for analysis.

**Assessment protocols**

**Conditioned pain modulation (CPM) assessment protocol**

***Test stimulus:***PPT will be used as the test stimulus, using an electronic digital algometer (Somedic AB, Sweden) as outlined above. It has been shown that PPT has a high intrarater reliability with excellent intraclass correlation coefficient (ICCs: 0.81-0.99) when measured at 4 different body sites (Waller et al. 2015). Participants will sit on a chair of adjustable height so the forearm is comfortably supported. PPT will be performed as outlined above on the two marked locations of the affected arm, which will be positioned in pronation on a table. PPT will be tested at baseline prior to cold water immersion, after 1 min during immersion, and 1 min post immersion. At each time point, PPT will be measured three times with 10-15 s rest intervals in between. The mean value of the three measurements at each point will be used for analysis.

***Conditioning stimulus****:* The Cold Pressor Test (CPT) will be used as a conditioning stimulus to elicit the CPM response. The unaffected hand will be submerged 4 inches above the wrist crease in a cold water bath, with a temperature maintained at 7°C for a period of 2 min (Locke et al. 2014). The water bath contains a mix of water and ice and it is supplied with a circulating pump to ensure uniformity of water temperature at the skin. The difference between PPT measurements taken before and after water immersion represents the CPM effect. This will be quantified as the percentage change in PPT relative to the baseline measure. Separate percentage change measures will be obtained for the wrist and elbow sites.

**Manipulation induced pain modulation (MIPM) assessment protocol**

The existence of a MIPM effect will be assessed using a very similar protocol to CPM testing.

***Test stimulus****:* PPT will be the test stimulus. The PFG test, ULNDT with radial nerve bias and measures of PPT at both test sites will be carried out at baseline and then repeated immediately after the conditioning stimulus (C5/6 contralateral lateral glide mobilisation). Testing will be performed with the participants lying supine on a plinth. PFG and UNLDT will provide additional measures of the MIPM effect.

***Conditioning stimulus*:**a grade III passive oscillatory, contralateral lateral glide (CLG) mobilisation of the C5/6 motion segment of the cervical spine will be used to induce MIPM (Vicenzino et al. 1996). The participant will be comfortably lying supine with arms by their side and instructed to report if they feel any discomfort or pain during execution of the mobilisation. In contrast to CPM this conditioning stimulus should be painless. The therapist will depress the scapulae with one hand, while the other hand cradles the occiput and neck above the C5/6 segment. Using the cradling hand, the therapist will apply a grade III passive oscillatory CLG directed towards the unaffected upper limb. The CLG stimulus will be performed for 60 s, and will be repeated three times, with 60-s rest periods in between (5 min total) (Vicenzino et al. 1996). The difference between PTT measurements taken before and after CLG mobilisation represents the MIPM effect. This will be quantified as the percentage change in PPT relative to the baseline measure. Separate percentage change measures will be obtained for the wrist and elbow sites and the PFG and ULNDT measures**.**

**Procedure**

Once eligibility criteria are confirmed, each participant will be asked to attend for preliminary assessment with CPM and MIPM assessment protocols in a single session. The CPM assessment protocol will be followed by the MIPM assessment protocol with a rest period of 15 min in between (subject to the findings from Pilot Study: HRE2016-0181). All outcome measures will be performed by the same researcher applying the CPT and CLG stimuli. All instructions will be standardized. Subjects will be asked to avoid physiotherapy and other forms of physical exercise on the day of assessment.

**Analysis**

Measures of CPM effect (% change PPT) and MIPM effect (% change PPT) will be obtained for the wrist and elbow sites. Null hypothesis 1 (i.e. no correlation between MIPM and CPM analgesic effects) will be tested using a Pearson’s correlation test to evaluate the association between change in PPT at both test sites during CPM and MIPM assessment protocols.

To test null hypothesis2subjects will be assigned post hoc into two groups, based on whether or not they demonstrate a meaningful CPM effect at the wrist test site. The assessment of meaningful CPM effect will be determined based on the criteria described by Locke et al. (2014). CPM effect will be considered meaningful if the percentage increase in wrist PPT from baseline is greater than the standard error of measurement (SEM) for repeated PPT measures. To compute the SEM, a pilot study (HRE2016-0181) of 10 participants will be conducted following the same PPT test-retest protocol (baseline, at 1 minute and at 2 mins) but without applying CPT. The SEM will then be calculated for each time point using the formula SD x √(1-ICC), where ICC represents the interclass correlation coefficient of the mean value for each time point. The SEM value will then be added to the PPT mean value to indicate the maximum upper value of normal variation in repeated PPT measures (Lock et al. 2014). This value will then be represented as a percentage change value. Therefore, any PPT percentage value above this percentage change value will indicate a meaningful CPM effect, greater than the normal measurement error. Subjects with a CPM effect above this percentage will be classified as CPM responders and those with a CPM effect below this percentage will be classified as CPM non-responders. In the study by Locke et al (2014) the meaningful CPM cut-off value was 5.3%, with approximately 10% of subjects found to be non-responders. It is anticipated that in this patient population this percentage of non-responders will be higher.

Once CPM effect groups have been determined, differences between the two groups for MIPM measures will be analysed. Percentage change in PPT at the elbow, PFG, and ULNDT (shoulder abduction), will be used to compare the MIPM effect between the CPM groups (i.e. CPM responder and CPM non-responder) using independent t-tests.

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