University of Alberta

Therapeutic Contextual Factors in Physiotherapy: Magnitude, Mechanisms and Contributors of Placebo Mediated Analgesia in Chronic Low Back Pain

by

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A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy
In
Rehabilitation Science

Faculty of Rehabilitation Medicine

Spring 2013
Edmonton, Alberta

DEDICATION

Dedicated to my family: my loving wife Andrea for being my company and a permanent source of encouragement in this long journey. Without her unyielding love and support this life project would have not been possible. To my children; Maximiliano, Agustina and my little one Dominga for inspiring me every day and reminding me what is important in life and what I should care about.

ABSTRACT

Mechanisms through which physiotherapy influence musculoskeletal pain include both the specific ingredient of an intervention as well as contextual factors inherent to clinical encounters including the therapist, patient and setting. These contextual factors are often termed “non-specific” or “psychosocial” effects and are associated with the placebo effect. Although well documented in other areas, the impact of contextual factors in treatment of low back pain (LBP) is unknown. In addition, the contributors to the physiotherapy placebo response in LBP have not been elucidated.

This project investigated the effect of contextual factors in patients with LBP receiving either active or sham interferential current therapy (IFC). Determinants of a favorable response to the contextual factors (i.e. placebo response) were also explored. A sample of 117 chronic LBP participants were randomly assigned into 4 groups: active limited (AL) included the application of active IFC in a limited therapeutic encounter (i.e. limited patient-practitioner interaction), sham limited (SL) included sham IFC in a limited therapeutic encounter, active enhanced (AE) included active IFC in an enhanced therapeutic encounter (i.e. supportive patient-practitioner relationship, encouragement), and sham enhanced (SE) included sham IFC in an enhanced therapeutic encounter. Outcomes included pain intensity (PI-NRS) and muscle pain sensitivity (PPT). Analysis included MANOVA, and logistic regression. In addition, clinical significance was determined.

Baseline data were similar. There were statistically significant differences between groups on PPTs and PI-NRS (baseline and after treatment). Mean differences in PI-NRS were 18.3 mm, 10.0 mm, 31.4 mm, and 22.2 mm, for the groups AL, SL, AE, and SE respectively. Clinically important effect sizes were found. Mean differences in PPTs were 1.2 kg, 0.3 kg, 2.0 kg, and 1.7 kg for the group AL, SL, AE, and SE respectively. Again, clinically important effect sizes were found. The level of therapeutic alliance and condition chronicity were the factors associated with the placebo response.

Results highlight the important role of contextual factors in the treatment of patients with chronic LBP. Enhanced therapeutic relationship was associated with meaningful clinical improvement. Also, perceived therapeutic alliance was found associated with placebo response. Factors other than the specific ingredient of a treatment may have a large role in achieving positive clinical outcomes, and exploring them is central to physiotherapy practice.

ACKNOWLEDGEMENTS

I would like to acknowledge a number of individuals who contributed to the successful completion of this thesis.

First of all, my sincere gratitude to my doctoral supervisors, Drs. Douglas P. Gross and David J. Magee for their competent and unfaltering guidance during my doctoral work. I am appreciative for their belief in my abilities and seeing that I was capable of this endeavour. Dr. Gross's helpful suggestions and criticism were essential to this thesis' completion. Thank you for being always accessible and for feeling I was a colleague rather than a student. Dr. Magee's endless support, encouragement and wisdom were also keys for the completion of this work.

Thanks are also extended to the members of my supervisory committee, Dr. Sharon Warren, Dr. Bruce Dick, and Dr. Saifee Rashiq for their generous feedback and for challenging me about my research. Special thanks to Dr. Sharon Warren for providing me the invaluable opportunity to work in the Research Center, and for always being there to share her research methodology expertise.

I am also grateful for Dr. Bruce Dick for his sincere interest in this thesis. His insightful comments and suggestions were really helpful to the development of this thesis. Also, I wish to thank Dr. Rashiq who donated his valuable time and expertise throughout the course of this thesis.

I would like to express my thanks to Dr. Anthony Joyce and Dr. Steven George who served as external examiners: Thank you for your time and effort on my behalf.

I am also greatly indebted to Dr. Susan Armijo, for sharing both her knowledge and her genuine friendship during all these years. Her assistance with this thesis, positive attitudes and partner for intellectually stimulation discussions about research and life made this path even more worth taking.

Also, I am extremely grateful to my research assistants Martha Funabashi and Maxi Miciak. The study would completely have failed without your support. Thank you for being always in a good mood and for adjusting your schedules to get the data collection done so quickly.

I would also like to thank Angela Libutti for her professionalisms, she helped me every time I need it.

Thank you to all subjects who volunteered their time to provide me with the experimental data. Their participation was fundamental to the success of this thesis.

I am also grateful for the financial support from the Department of Physical Therapy, the Faculty of Rehabilitation Medicine, the University of Alberta, and the Physiotherapy Canadian Association.

Above all, I would like to thank Andrea, my wife for her love, encouragement, and understanding throughout the years.

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION, DEFINITION OF TERMS, OBJECTIVES, HYPOTHESES, LIMITATIONS AND DELIMITATIONS OF THE RESEARCH

Page

CHAPTER 2
LITERATURE REVIEW

Page

CHAPTER 3

EFFECTIVENESS OF INTERFERENTIAL CURRENT IN THE MANAGEMENT OF MUSCULOSKELETAL PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Page

CHAPTER 4
A PRELIMINARY INVESTIGATION INTO THE EFFECTS OF ACTIVE INTERFERENTIAL CURRENT THERAPY AND PLACEBO ON PRESSURE PAIN SENSITIVITY: A RANDOM CROSSOVER PLACEBO CONTROLLED STUDY. A PILOT STUDY.

Page

CHAPTER 5
ENHANCED THERAPEUTIC RELATIONSHIP MODULATES PAIN INTENSITY AND MUSCLE PAIN SENSITIVITY IN PATIENTS WITH CHRONIC LOW BACK PAIN: A RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL.

Page

CHAPTER 6
CONTRIBUTORS TO PLACEBO MEDIATED ANALGESIA IN CHRONIC LOW BACK PAIN

Page

CHAPTER 7
GENERAL DISCUSSION AND CONCLUSIONS

Page

8. APPENDICES

Page

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

ACC	*Anterior Cingulate Cortex*
AMF	*Amplitude Modulated Frequency*
ANOVA	*Analysis of Variance*
CCK	*Cholecystokinen*
CEQ	*Credibility and Expectancy Questionnaire*
CLBP	*Chronic Low Back Pain*
DLPFC	*Dorsolateral Prefrontal Cortex*
fMRI	*Functional Magnetic Resonance Image*
GRS	*Global Rating Scale*
HZ	*Hertz or cycles per second*
ICC	*Intraclass Correlation Coefficient*
IFC	*Interferential Current Therapy*
K	*Kappa Statistics*
MANOVA	*Multivariate Analysis of Variance*
MD	*Mean Difference*
MID	*Minimally Important Difference*
NSLBP	*Nonspecific Low Back Pain*
ODI	*Oswestry Disability Index*
OR	*Odds Ratio*
P	*p value*
PET	*Positron Emission Tomography*
PI-NRS	*Pain Intensity Numerical Rating Scale*
PRES	*Pain Rehabilitation Expectations Scale.*
RCT	*Randomized Controlled Trial*
SD	*Standard Deviation*
SPSS	*Statistical Package for Social Sciences*

TA	*Therapeutic Alliance*
TAC	*Tomography Axial Computerized*
TENS	*Transcutaneous Electrical Nerve Stimulation*
VAS	*Visual Analogue Scale*

“The good physician treats the disease; the great physician treats the person who has the disease”

Sir William Osler

CHAPTER 1

INTRODUCTION, DEFINITION OF TERMS, OBJECTIVES, HYPOTHESES, LIMITATIONS AND DELIMITATIONS OF THE RESEARCH

1.1. INTRODUCTION

For a more integrated, effective and client-centered therapy, physiotherapy demands a comprehensive analysis of all factors that potentially could influence the clinical efficacy of its treatments. Aside from the correction of physical impairment, or from the specific ingredient of an intervention, several other variables may influence clinical outcomes. Mechanisms through which physiotherapy interventions influence musculoskeletal pain are likely complex and include contextual factors related to the therapist, patient and setting. These contextual factors are often termed "non-specific" or "psychosocial" effects.[1] Non-specific effects are those not specific to the active ingredient of the particular treatment used but are associated with the process of its provision and reception. Non-specific effects are not expected to lead to positive therapeutic outcomes on the basis of the rationale underlying the specific treatment, but represent the context in which the intervention is applied. [2-4]

Contextual factors include such things as the clinician's words, the hospital or clinical atmosphere and environment, color or appearance of the intervention/pill, the clinician-patient interaction, the nature of the therapist's uniform, and the appearance and sight of the therapeutic equipment among other factors.[2-4] It is

within this treatment environment or therapeutic encounter that the placebo effect operates. When contextual factors produce a positive effect on clinical outcomes, this is known as the "placebo effect". Thus, the terms "contextual effects", "non-specific effects", and "placebo effects" are synonymous and have been used interchangeably.[3] The study of the placebo effect is, in essence, the study of the psychosocial context that surrounds the patient during treatment.[2, 4]

Although in clinical practice both effects work together to benefit patients, the estimation of the placebo effect, or contextual factors that surround a therapy has not traditionally been a primary focus of investigation. Regulatory requirements for clinical researchers encourage study designs demonstrating specificity of the active ingredients of a treatment. [5, 6] In modern medicine, placebo is normally considered a simple baseline against which evaluation of efficacy of an intervention occurs. Furthermore, in clinical trials, the placebo effect is judged as an artefact that interferes with the true effect of the treatment of interest.[7] However, objective and measurable physiologic functions such as concentrations of hormones, heart rate, and cerebral electrical activity [8-10] as well as subjective outcomes (e.g. pain)[11-13] have been changed after exposure to placebo interventions. In addition, there is evidence that the placebo effect along with the active treatment may influence results of clinical trials.[5, 14-16] Thus, placebo has evolved from its original pejorative connotation in clinical research to a relevant target of scientific inquiry and a key therapeutic ally. Yet disappointingly, despite the growing interest in studying its effect, very little is known about how the placebo or psychosocial context operates when physiotherapy interventions are

applied. More specifically, evidence of the magnitude of this phenomenon and the predictors of placebo analgesia in chronic pain patients receiving physiotherapy is still absent. Chronic pain is a major cause of morbidity, with the low back being one of the most common locations of symptoms.

Chronic low back pain is a highly prevalent problem that represents a challenge for health care providers, including physical therapists, and society.

An intervention commonly used by physical therapists in the treatment of individuals with low back pain is interferential therapy (IFC).[17] In chronic low back pain, IFC combined with other interventions was shown to be more effective than placebo application at 3-month follow-up[18]

Understanding how therapeutic context influences clinical outcomes in chronic pain is relevant. It has been reported that common non-pharmacological interventions (e.g. transcutaneous electrical nerve stimulation, manual therapy) used by physiotherapists to treat non-specific chronic low back pain display similar and modest short-term benefit for these interventions but little long-term benefit. [19, 20] Also, the outcome literature suggests that only a minority of patients show measurable benefit from any of the treatments commonly given for this condition.[21] Given that comparable effects have been observed across very different therapies, this equivalent effect is not likely to be explained by specific mechanisms inherent to the therapies[22]. A novel area showing potential to answer this question is found in the study of the contextual factors inherent to clinical encounters.

Thus, this project aimed to evaluate: 1. the impact of the therapeutic context (i.e. placebo effect) in both active and sham IFC intervention in patients with non-specific chronic low back pain. Emphasis was focused on determining the differences in pain perception and muscle pain sensitivity between active IFC applied using a limited therapeutic context (i.e. limited patient-practitioner interaction) and active IFC applied using an enhanced therapeutic context (i.e. supportive patient-practitioner interaction, encouragement). In the same way, differences in pain perception and muscle pain sensitivity between sham IFC applied using a limited therapeutic context (i.e. limited interaction) and sham IFC applied using an enhanced therapeutic context (i.e. supportive patient-practitioner interaction, positive rapport, encouragement, etc.) were assessed.

2. This project also enabled the researchers to explore predictors of a favourable response to the contextual factors (placebo) in this study sample. We investigated a variety of potential predictors including personal (ie. age, gender), psychosocial (i.e. therapeutic alliance), and condition-related factors (i.e. pain intensity, disability).

1.2. DESCRIPTION OF CHAPTERS

1.2.1. CHAPTER 2. LITERATURE REVIEW

In this chapter, pertinent information about the intervention used in this project (interferential current therapy), as well as the clinical condition of interest (non-specific chronic low back pain) is included.

This chapter also provides a comprehensive examination of the placebo effect including its concept, mechanisms, neurobiology, magnitude, and predictors. In addition, special emphasis was put on the role of therapeutic alliance as a potential contributor to successful treatment. In addition, gaps of knowledge as well as areas needing additional quality research were identified. Finally, clinical implications about the therapeutic analgesic potential of the psychosocial context (i.e. placebo) in physiotherapy practice are presented.

1.2.2. CHAPTER 3. EFFECTIVENESS OF INTERFERENTIAL CURRENT THERAPY (IFC) IN THE MANAGEMENT OF MUSCULOSKELETAL PAIN: SYSTEMATIC REVIEW AND META-ANALYSIS

IFC was chosen as the physiotherapy intervention for this project. Because the effectiveness of IFC as a pain modulator in musculoskeletal pain has been matter of discussion, we attempted to clarify this issue through a systematic review and meta-analysis. Full presentation of this article is included in this chapter, this article has also been published elsewhere (See Fuentes et al., Physical Therapy 2010; 90 (9): 1219-38).

1.2.3. CHAPTER 4. A PRELIMINARY INVESTIGATION INTO THE EFFECTS OF ACTIVE INTERFERENTIAL CURRENT THERAPY AND PLACEBO ON PRESSURE PAIN SENSITIVITY: A RANDOMIZED CROSSOVER PLACEBO CONTROLLED STUDY. A PILOT STUDY

This chapter describes a pilot study conducted under experimental conditions to determine feasibility of our methodology and measurement techniques. This investigation was a random crossover placebo controlled study conducted under laboratory conditions. A mechanical model of pain was applied to a sample of forty healthy volunteers (female and male) to evaluate and to compare the effects of active IFC intervention, placebo IFC intervention and a control condition on muscle pain sensitivity. In this pilot study, the hypoalgesic effects of active and placebo IFC, and the contributors associated with the placebo response, were determined. This chapter has been published (See: Fuentes et al., Physiotherapy 2011; 97: 291-301).

1.2.4. CHAPTER 5. ENHANCED THERAPEUTIC RELATIONSHIP MODULATES PAIN INTENSITY AND MUSCLE PAIN SENSITIVITY IN PATIENTS WITH CHRONIC LOW BACK PAIN: A RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL

The positive impact of therapeutic contextual factors, particularly the therapeutic alliance, in medicine and psychology has been well documented; however, very little is known about how the manipulation of the therapeutic alliance influences clinical outcomes in physiotherapy. This study provides some insight into this

matter. The impact of this construct (alliance) on pain intensity and muscle pain sensitivity in chronic low back pain was evaluated in a randomized double-blind controlled trial. In this chapter, the main findings of this study are presented, emphasising the magnitude of the observed effects and clinical significance of the results. Clinical implications for physiotherapy practice are also discussed.

1.2.5. CHAPTER 6. THE CONTRIBUTORS TO THE PHYSIOTHERAPY PLACEBO RESPONSE IN CHRONIC LOW BACK PAIN

Predictors of the physiotherapy placebo response in chronic low back pain have not been elucidated. Therefore, this study attempted to clarify the role of diverse contributors to the placebo response for patients with chronic low back pain receiving physiotherapy. In this study, diverse potential predictors were considered, including personal (i.e. gender, age), psychosocial (i.e. therapeutic alliance, expectancy), and clinical (i.e. pain intensity, disability, chronicity) variables. Results of this study are displayed in this chapter and implications for treatment are outlined.

1.2.6. CHAPTER 7. GENERAL DISCUSSION AND CONCLUSIONS

In this chapter, key findings from the studies included in this project are summarized. Special emphasis is placed on describing the clinical significance of the results and the contributions/implications for physiotherapy practice.

1.3. DEFINITION OF TERMS

a) *Contextual effect*: those effects related to the diverse psychosocial elements that surround a patient when a therapeutic treatment is delivered. Contextual factors include such things as the clinician's words, the environment in which the treatment is given, the sight of a therapeutic apparatus, the clinician-patient interaction, verbal suggestions, and the "white coat phenomena" among others.[14, 15] Since the administration of a placebo is associated with the psychosocial therapeutic context, these two terms may be used interchangeably.[3, 14, 16]

b) *Contextual responder*: An individual who has a change in a symptom or condition due to the therapeutic contextual factors (e.g. clinician's words, the clinician-patient interaction, verbal suggestions, white coats) that surround the administration of an inert treatment. Due to the association between placebo and the psychosocial context, the term placebo responder and contextual responder may be used interchangeably.

c) *Interferential current therapy (IFC):* a common electrotherapeutic modality used frequently by physiotherapists to treat musculoskeletal pain.[17, 23, 24] IFC may be described as the application of alternating medium-frequency electrical current (normally 4000 Hz) amplitude modulated at low frequency (0 to 250 Hz) for therapeutic purposes. [25, 26]

d) *Non-specific effect:* those effects elicited in response to any concomitant element included in the clinician-patient encounter (e.g. clinician's words, color of the pill, clinician-patient relationship, white coats, etc.) that are applied along with the specific ingredient.[27] Non-specific effects are those that are not expected based on the physiological rationale underlying the treatment. These factors represent the context in which the intervention is applied[3, 4, 14] Thus, the terms "contextual effect", "non-specific effect", and "placebo effect" are synonymous and may be used interchangeably.[3]

e) *Non- specific low back pain (NSLBP):* is described as pain, muscle tension, or stiffness localized below the costal margin of the back and above the inferior gluteal folds, with or without radiating leg pain, but with no clearly identifiable tissue damage or pathology [28]. When it persists for 12 weeks or more, the condition is often defined as non-specific chronic low back pain[28] . NSLBP is a diagnosis of exclusion, as the term implies that the condition is not attributed to a specific pathology or disease process.[19, 28]

f) *Placebo analgesia:* the occurrence of an analgesic effect in the absence of an active analgesic agent/ingredient (e.g. drug).[29]

g) *Placebo effect*: a beneficial physiological or psychological change associated with the application of an inert substance, sham procedure or

treatment known to have no therapeutic effect for the specific condition being treated, or in response to therapeutic encounters and symbols. [4-6, 30] A placebo effect is a positive therapeutic context effect, with the power to influence the therapeutic outcome. [4, 30, 31]

h) *Placebo responder:* An individual who responds to an inert substance, sham procedure or treatment known to be without any therapeutic effect for the specific condition being treated, or in response to therapeutic encounters and symbols. [4-6, 30]

i) *Placebo response*: a change in a symptom or condition of an individual caused by [27, 30] the application of an inert substance, sham procedure or treatment known to be without any therapeutic effect for the specific condition being treated, or in response to therapeutic encounters and symbols. [4-6,34]

j) *Specific effect*: In the application of any treatment, the physiological or specific effects are those that are believed to influence the underlying disease or physical impairment as a result of theoretical or biological rationale.[1]

k) *Therapeutic alliance (also called the patient-practitioner relationship)*: is the working rapport or positive social connection between the patient and the clinician.[32]

1.4. OBJECTIVES OF THE STUDY

The specific objectives of this project were:

1. To determine the magnitude of the therapeutic context (i.e. placebo effect) during the application of active IFC intervention in patients with chronic low back pain, comparing the effect of a limited therapeutic context (i.e. limited interaction) and an enhanced therapeutic context (i.e. supportive patient-practitioner relationship, encouragement) on pain intensity and muscle pain sensitivity.
2. To determine the magnitude of the therapeutic context (i.e. placebo effect) during the application of sham IFC intervention in patients with chronic low back pain, comparing the effect of a limited therapeutic context (i.e. limited interaction) and an enhanced therapeutic context (i.e. supportive patient-practitioner relationship, encouragement) on pain intensity and muscle pain sensitivity.
3. To quantify the extent to which the enhanced therapeutic context modifies pain intensity and muscle pain sensitivity in the active IFC and sham IFC intervention groups.

4. To explore the determinants associated with a favorable response to the contextual factors (i.e. placebo response) in patients with chronic low back pain.

1.5. RESEARCH HYPOTHESES

The following hypotheses were investigated in this study:

1. Active IFC, applied in an enhanced therapeutic context, will statistically and to a clinically important extent reduce pain intensity scores in patients with chronic low back pain, when compared to active IFC applied in a limited therapeutic context.
2. Active IFC, applied in an enhanced therapeutic context, will statistically and to a clinically important extent decrease muscle pain sensitivity in patients with chronic low back pain, when compared to active IFC applied in a limited therapeutic context.
3. Sham IFC, applied in an enhanced therapeutic context, will statistically and to a clinically important extent reduce pain intensity score in patients with chronic low back pain, when compared to sham IFC applied in a limited therapeutic context.
4. Sham IFC, applied in an enhanced therapeutic context, will statistically and to a clinically important extent decrease muscle pain sensitivity in patients with chronic low back pain, when compared to sham IFC applied in a limited therapeutic context.

5. Active IFC and Sham IFC, applied in an enhanced therapeutic context, will statistically and to a clinically important extent decrease muscle pain sensitivity in patients with chronic low back pain when compared to baseline scores.
6. Positive therapeutic alliance, high expectations of pain relief, moderate baseline pain intensity, and a moderate level of disability will predict positive response to the contextual factors (i.e. placebo response) in patients with chronic low back pain.
7. Sham IFC, applied in an enhanced therapeutic context, will statistically and to a clinically important extent reduce pain scores in patients with chronic low back pain to the same extent as active IFC applied in a limited therapeutic context.

1.6. LIMITATIONS OF THE STUDY

This study was limited by:

a) The ability of the researcher to apply the same procedure to every subject. The possible confounders to be controlled were:

i) IFC electrode placement: the reference for placement electrodes was the same for every subject (lumbar area).

ii) Measurement bias was controlled by the use of a valid and reliable test instrument (algometer) and questionnaires. In addition, the evaluator had expertise in the use of the

algometer. He has been responsible for algometric measurements in two previous projects. Therefore, consistent measurements were achieved during the experimental procedure.

iii) The algometer and the area of application was the same for all subjects (landmarking was used to allow easy recognition of the point of the algometer application).

iv) The algometer was calibrated every week for the duration of the experimental procedure in order to ensure that the force rate being applied was consistent (1 k/cm^2/seg).

v) The same evaluator was blinded for the assessment of all subjects.

vi) The instructions were the same for every subject and were based on a videotaped script.

vii) Clinicians used in this study were trained in methods of patient-therapist interactions to ensure they were able to create the two different therapeutic contexts. Clinicians were instructed in advance on the scripts for their interactions with the active and sham groups by means of a training manual and by role-playing with simulated patients.

b) The ability to generalize the results because of the use of a convenience sample.

c) This research was applicable only in the following conditions:

i) Under the same conditions and procedures performed in this study.

ii) Only for the area over the erector spinae muscle in patients with non-specific chronic low back pain.

1.7. DELIMITATIONS OF THE STUDY

This study was delimited to:

Subjects between 18 and 60 years old, having non-specific chronic low back pain.

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CHAPTER 2

LITERATURE REVIEW

2.1. NON-SPECIFIC LOW BACK PAIN

Non-specific low back pain (NSLBP) is described as pain, muscle tension, or stiffness localized below the costal margin of the back and above the inferior gluteal folds, with or without leg pain (sciatica).[1] When it persists for 12 weeks or more, the condition is defined as chronic low back pain.[2] NSLBP is a diagnosis of exclusion; the term implies that the condition is not attributed to a specific pathology or disease process. [2, 3] NSLBP is a highly prevalent problem that represents a challenge for health care providers and society. For example, in developed countries, more than 90 percent of adults will experience this condition at some stage of their lives.[4, 5] In addition, each year, 15 to 45 percent of adults suffer low back pain, [6] and frequent recurrence has been reported up to two years later. [7, 8] Disability and work absence associated with chronic low back pain involves millions of dollars worldwide due to the impact on productivity, compensation payments, treatment costs, and resource utilization.[5, 9] The economic burden associated with chronic NSLBP is considerable for patients, health systems and society. However, the impact of NSLBP is not only economic and societal; it also implies an important level of human suffering seriously affecting the quality of life for some patients.[10]

Common non-pharmacological interventions used by physiotherapists to treat chronic NSLBP include acupuncture, massage, thermotherapy, manipulation, laser therapy, and electroanalgesia (e.g. transcutaneous electrical nerve stimulation or interferential therapy). The results of recent systematic reviews and meta-analyses have shown similar and modest short-term benefit for these interventions when treating chronic low back pain, but little long-term benefit.[3, 11]

Given that comparable effects have been observed across very different therapies (e.g. IFC, manual therapy, exercise, and massage therapy), this comparable effect is not likely to be explained by specific mechanisms inherent to the therapies. Potentially the modest yet nearly equivalent effects could be due to common factors (i.e. patients' expectancies and beliefs, patient-therapist relationship) across the different therapeutic contexts, as opposed to a specific mechanism.[12] In addition, it is also possible that the limited results demonstrated by these treatments are because the applications of these interventions during clinical trials did not encourage the non-specific or contextual factors associated with treatment delivery required to enhance clinical outcomes. However, these explanatory hypotheses are merely speculative and certainly need to be confirmed through future research.

2.2. INTERFERENTIAL CURRENT THERAPY

Interferential current therapy (IFC) is a common electrotherapeutic modality regularly used by physiotherapists to treat musculoskeletal pain [13-15]. IFC may be

described as the application of alternating medium-frequency electrical current (normally 4000 Hz) amplitude modulated at low frequency (0 to 250 Hz) for therapeutic purposes [16, 17] A claimed advantage of IFC over low-frequency currents (i.e. Transcutaneous Electrical Nerve Stimulation- TENS) is its capacity to diminish the impedance offered by the skin and subcutaneous tissue [16]. Thus, by diminishing the skin resistance, the discomfort normally incurred by traditional low-frequency currents is reduced. [17]

2.3. IFC AS ISOLATED INTERVENTION IN CHRONIC LOW BACK PAIN

In clinical settings, IFC is regularly applied as a co-intervention along with other therapeutic alternatives such as exercise, manual therapy, and ultrasound [18]. However, it is evident that under this scenario, the effect of IFC may be confounded by the other therapeutic interventions. Results of a recent systematic review and meta-analysis of IFC on musculoskeletal pain [18] revealed that only two studies have been conducted to determine the clinical analgesic effectiveness of IFC as a single therapeutic modality on chronic LBP. [19, 20] However, these two studies contrasted the effect of IFC versus other therapies such as massage and lumbar traction[20] or versus different IFC stimulation parameters. [19] Therefore, no placebo or control condition was included. Consequently, the results and conclusions emerging from these studies about the analgesic effectiveness of IFC are questionable.

Thus, the question of whether IFC as an isolated technique has a positive effect on pain reduction in chronic LBP still remains. To produce a satisfactory answer to this question, a control or placebo group must be necessarily incorporated into future study designs.

2.4. PLACEBO: HISTORICAL AND CONCEPTUAL BACKGROUND

The placebo effect has been defined as beneficial physiological or psychological changes associated with the application of an inert substance, sham procedure or treatment known to have no therapeutic effect for the specific condition being treated, or in response to therapeutic encounters and symbols.[21] Placebo analgesia is defined as the occurrence of an analgesic effect in the absence of the active analgesic agent/ingredient (e.g. drug).[22] Placebo analgesia is also defined as a reduction in perceived pain intensity following a physiologically "inert" treatment as compared to a no-treatment natural history condition or control group.[22] The placebo effect does not arise because of the inertness of the treatment. Since the treatment is administered within a context (e.g. clinician's words, the clinician-patient relationship, the therapist's uniform, and/or the appearance of the therapeutic equipment, etc.), it is the context that likely plays a relevant role.[23] Thus, the placebo covers more than an intervention. Rather, it includes complex phenomena encompassing individual patient and therapist characteristics, features of the patient-clinician relationship (e.g. beliefs, expectations), and attributes regarding the setting and environment in which the treatment is carried out.[23] It has been postulated that the combined action of these features over the course of

the treatment can enhance the patient's health resulting in beneficial effects.[23] Indeed, the study of the placebo effect examines the psychosocial context surrounding the patient and the impact that this context has on the patient's experience and the clinical outcomes of the treatment.[24-33]

Historically, placebos have been associated with inert agents or interventions with the aim being to please the patient rather than eliciting a therapeutic effect. [34-36] In fact, placebo is the first person future indicative of the Latin *Placere*. Thus, the word placebo translates to "I will please".[35-37] The view that placebo interventions only could comfort patients was maintained until the 1950s.

In the second quarter of the 20th century, the discovery of effective drugs and the introduction of randomized control trials (RCT) as the gold standard for clinical trials changed perspectives about the placebo.[37] In the RCT paradigm, placebo was included as a mere comparison or a baseline against which to demonstrate the effectiveness of a drug or intervention. Thus, placebo was considered as an artefact interfering with the true effect of the treatment of interest or a kind of "noise" that needed to be subtracted out in the data analysis. [35, 36, 38] Under this scenario, placebo responses were given a kind of "second-order physiology that floats like oil on water on top of the *fundamental physiological changes* associated with the active treatment"[38] (p. 3, emphasis added). This belief has changed considerably of late, since neurobiological and psychological mechanisms of the placebo effect have begun to be identified. For example, subjective outcomes (e.g. pain) [24, 26, 39]and objectively measurable physiologic function changes have been observed in response to placebo interventions in

different conditions including immune,[40] endocrine,[41] respiratory and cardiovascular systems,[31] Parkinson's disease,[30, 42] and depression.[43, 44]

In addition, neuroimaging studies have revealed two important findings. First, that placebo-induced analgesia decreases neural activity in pain processing areas of the brain, and second, that placebo and endogenous opioid peptides share the same network. [45-47] Thus, these data confirm that placebo is more than a response bias, rather it represents a real phenomenon capable of producing biological effects on the body and brain.

The conceptualization of a placebo and the rationale behind it has therefore evolved from being an inert intervention, intended just to please the patient or being considered a mere clinical baseline in the biomedical model in medicine, to an overall stimulation of a positive therapeutic intervention with the capability to exert positive therapeutic effects.

2.5. MECHANISMS OF PLACEBO EFFECT

Substantial evidence suggests that the placebo effect is a complex psychobiological phenomenon mediated by a variety of psychosocial and neurobiological factors.[26, 28, 29, 32, 33, 41, 48-50] The mechanisms of placebo analgesia that have generated the majority of research are conditioning, expectations and learning. Given the complex features of the placebo process, it is unlikely that a single mechanism is operating. Moreover, it is postulated that conditioning is complemented by expectancies, making it difficult to disconnect the relative contributions of each. Thus, these factors are not mutually exclusive and

commonly operate in combination to elicit the placebo's analgesic response. In the same way, when the two processes are combined, the placebo effect is largest when compared to conditioning alone or expectation alone.[28, 48] Placebo responses are mediated by conditioning when unconscious physiological processes such as hormone secretion are involved, whereas when conscious processes such as pain come into play, the placebo responses are mediated by expectations.[41]

2.5.1. EXPECTATIONS

The expectation of a therapeutic effect is considered a foundational concept in placebo analgesia.[29, 32, 33, 48, 50-52] Expectancies represent a conscious process associated with observational learning, previous experiences and persuasion [53, 54] Under conditions in which patients have expectations that pain relief will occur with the application of an intervention, pain reduction may occur as a result of psychological factors.[32, 48, 55]

In the same way, it has been shown that expectations can be verbally induced. Thus, the inclusion of convincing verbal instructions about the analgesic efficacy/effectiveness of a particular treatment can contribute to positive expectations influencing treatment outcomes. [41, 53, 56]

In physiotherapy, experimental evidence suggests that positive expectancies of pain relief are a major contributor to successful electroanalgesia treatment. [57, 58] Also, the patient's expectations seem to be important in predicting outcomes in patients with low back pain receiving physiotherapy and cognitive-behavioural treatments. [59, 60] Hence, the informational context of telling subjects that a

normally applied physiotherapy therapeutic intervention (e.g. ultrasound, electrotherapy or laser) is intended to diminish pain might activate appropriate expectancies of pain relief.

Based on the link between the opioid sensitive pain modulating network and the cortex and limbic system, it is plausible that emotional conditions and expectations could positively reduce pain perception under placebo interventions. This has been demonstrated where the administration of a placebo, in combination with the verbal suggestion that the placebo is a painkiller (i.e. verbal context), was able to reduce pain by both opioid and non-opioid mechanisms.[48] Moreover, recent brain-imaging evidence has shown that placebo-induced expectations of analgesia increased activity in the prefrontal cortex in anticipation of pain and decreased the brain's response to painful stimulation.[45]

Similarly, various authors,[25, 52, 61-63] have highlighted the role of expectations in the modulation of pain. For example, in post-operative pain following oral surgery [62, 63] and thoracic surgery,[61] authors applied active drugs through covert infusions by computer-controlled machines (without a nurse or doctor in the room) instead of using an open injection. Since patients were unaware that an analgesic treatment was carried out, expectations of pain reduction were eliminated. When compared to open injection (expectations remained intact), the hidden one was significantly less effective. Thus, the analgesic dose of painkillers required to reduce the pain by 50% was much higher for hidden infusions than for open ones. [61] In the same way, a hidden injection of 6-8 mg of morphine was found to have the same effect to an open injection of saline solution (placebo) in full view of the

patient. [62, 63] This evidence confirms that expectations of pain relief are a crucial factor in pain modulation, and emphasizes the role of the psychosocial component of a therapy (i.e. placebo). This also raises an interesting question regarding how the role of enhanced expectations can affect clinical outcomes in both active and sham physiotherapy interventions.

2.5.2. CONDITIONING

Some lines of evidence suggest that a placebo response is partly explained by classical Pavlovian unconscious conditioning based on learning and repeated association.[49, 64] When an unconditioned stimulus (e.g. interferential therapy or active agent inside a pill) is delivered along with conditioned stimuli (i.e. context; the clinical setting, words, the white coat, or impressive looking equipment), this can lead to a conditioned response (i.e. analgesia). The pairing of one or more of these associated conditioned stimuli with previous successful therapeutic experiences is believed to play an important role in pain relief.[49, 56, 65, 66] Thus, with prior experience or associations with an effective analgesic therapy, the application of a subsequent placebo that physically resembles the initial active component may create positive analgesic effects. These contextual factors, representing the conditioned stimuli, are capable of producing analgesic responses when the active agent is absent. This hypothesis has been confirmed by some studies. For example, Voudouris et al.1985, 1989 [67, 68] in a series of investigations applied a protocol in which conditioning was achieved by pairing a placebo analgesic cream with a painful stimulus that was secretly reduced with respect to a

baseline condition to make the subjects believe that the cream was indeed effective. The subjects in the conditioned group (placebo cream) showed a larger pain relieving effect than the unconditioned group. In addition, in crossover studies, patients who received the active ingredient first (e.g. analgesic) reported a stronger effect than those who received the placebo first. [69-71] These studies revealed that when a placebo drug was given as a second treatment, it was more effective as an analgesic when it followed a more potent analgesic. This evidence suggests that a previous experience with an analgesic drug may enhance the analgesic effectiveness of a subsequent placebo via a conditioning process.

2.5.3. OBSERVATIONAL LEARNING

There are indications that prior positive experience plays a key role in maximizing both behavioral and neurophysiological placebo responses.[72] In addition, it has been reported that placebo analgesia is stronger when pre-conditioning with effective analgesic treatments is performed. [73] Taken together these reports suggest that the placebo response is a learning phenomenon. Recent literature[26] has also investigated the effect of observation on the placebo response. In this study, substantial placebo effects occurred without actual first-hand experience. Subjects were able to experience placebo responses following observation of another subject undergoing a beneficial treatment.

More interesting, the magnitude of the effect was similar between subjects who directly experienced the benefit through conditioning to those who just observed

the benefit.[26] It was suggested that this observational learning could convey information that was crucial to build up expectation of benefits.[74]

These behavioral observations highlight the fact that contextual cues and the therapeutic context around the delivery of the treatment are relevant for the induction of positive expectations and placebo effects. In addition, these findings show that placebo analgesia is finely tuned by social observation and suggest that different forms of learning take part in the placebo phenomenon.[26]

2.6. NEUROBIOLOGY OF THE PLACEBO EFFECT

Extensive research has been performed to elucidate the underlying mechanisms behind placebo analgesia[21, 75]. Today it is acknowledged that placebo analgesia is mediated by both endogenous opioid and non-opioid mechanisms (e.g. serotonin). This evidence comes from several studies based on neuropharmacological approaches using an opioid antagonist (naloxone) [48, 76, 77]. In these studies, placebo-induced reductions of experimental and clinical pain were reversed by naloxone. A second study model that complements this line of research using naloxone is based on investigations of the endogenous peptide cholecystokinen (CCK). CCK is released along with endogenous opioids competing with their analgesic effects (i.e. inhibitor of endogenous opioid). Proglumide is a nonselective antagonist of CCK receptors. Therefore, the application of proglumide might augment the placebo analgesia. Studies have shown that the blockage of CCK enhances the placebo analgesic effect. [21, 75] Thus, placebo analgesia appears to be the result of a balance between endogenous opioids and

endogenous CCK.[25] The results of a trial in chronic back and leg pain also confirm the role of opioids in the placebo-induced analgesia phenomenon. In this study, placebo responders showed a higher concentration of endorphins in the cerebrospinal fluid than non-placebo responders.[78] However, other evidence suggests that the non-opioid system also plays a role in placebo analgesia. For example, when a placebo is induced by prior conditioning with a non-opioid drug, the analgesic effect was not reversed by naloxone.[48]

Although the studies described above present pharmacological confirmation about the biochemical events associated with placebo analgesia, they do not provide data about the neural mechanisms or the specific brain regions involved in this phenomenon. Recent studies using novel technology such as positron emission tomography (PET) [46] and functional magnetic resonance imaging (fMRI) [45, 47] have allowed the identification of the specific brain regions activated in response to placebo analgesia. These studies have shown that placebo effects are associated with a reduction in neural activity in areas known to process symptoms such as anxiety and pain. Similarly, these reductions are accompanied by increases in neural circuitry activity in areas involved in emotional regulation.

fMRI and PET imaging studies comparing the effects of placebo and opioid-induced analgesia have shown that placebo analgesia resembles opioid treatment and is associated with altered brain activity in pain-sensitive brain regions. [45] For example, Watson et al. 2009 [47] found that a common fronto-cingulate network (i.e. medial frontal cortex, dorsolateral prefrontal cortex, and anterior mid-cingulate cortex) was activated in placebo analgesia and placebo conditioning.

Also, fMRI imaging experiments have shown that reduced pain ratings during placebo analgesia were paralleled by decreased neural activity in pain processing areas of the brain such as the thalamus and the anterior insular cortex.[45] From these studies it appears that that the altered pain perception during placebo results from active inhibition of nociceptive input and not simply from report bias.

In addition, Petrovic et al. 2002 [46] and Wager et al. 2004 [45] found that similar regions of the brain were activated by both a placebo administration and a narcotic drug. These imaging studies provide direct support that the placebo-induced analgesia and endogenous opioid peptides share the same network. This opioid network is associated with a descending pain modulating pathway (i.e. "top-down" pain regulation) involving the cerebral cortex with the midbrain. Relevant opioid-mediated structures of this network include the anterior cingulate cortex, the periaqueductal grey matter, the parabrachial nuclei in the brainstem, hypothalamus, amygdala, and the dorsal horn at the spinal cord.

In addition, recent evidence has confirmed the involvement of the spinal cord in placebo analgesia.[79] Pain-related activity in the ipsilateral dorsal horn to the painful stimulation was reduced under placebo, suggesting that spinal inhibition can also play a role in the placebo analgesia mechanisms.

In summary, mechanisms of opioid and placebo analgesia reveal a shared neural network. Placebo analgesia relies on the up-regulation of the pain-modulating areas and involves a top-down activation of endogenous analgesic activity via the descending modulatory system. The level of the afferent nociceptive activity in

which this modulation occurs is likely to be the spinal cord, possibly mediated by the descending pain control system.

2.7. POWERFUL OR POWERLESS? THE MAGNITUDE OF THE PLACEBO EFFECT

The magnitude of placebo analgesia effects has been under scrutiny. The results of various meta-analyses have shown different magnitudes of the placebo effect leading to diametrically opposing positions with regards to the power of the placebo effect. [22, 80-86] In addition, recently some concerns regarding the susceptibility to bias when interpreting the clinical relevance of this phenomenon have been raised.[87]

In his classic and influential paper entitled "The powerful placebo", Beecher 1955,[88] concluded that the application of placebo intervention was associated with significant improvement in 35.2 percent of patients with various medical conditions for which outcome responses were subjective. Because the focus of medicine at that time was mainly related to the detection of specific treatment effects instead of the study of the placebo phenomenon, Beecher's conclusion was not a topic for further inquiry and was considered as "truth" for decades. Thus, for many years, placebo effects of treatment were considered to contribute a fixed fraction (one third) of any treatment's outcomes. However, recently some authors have argued, based on several methodological flaws in this original paper, that the size of the placebo effect reported has been overestimated.[80, 81, 89, 90] Therefore, the commonly held clinical belief about the fixed fraction was erroneous. As an

example of the methodological flaws in Beecher's study, the improvement reported accounted only for subjects who received a placebo intervention and had positive effects. Moreover, the analysis did not consider the subjects who had negative outcomes after receiving placebo. Also, the results were based on within-group analysis and the data lacked any control for the natural history of the condition and other factors such as the regression to the mean. Thus, these confounding factors could not be excluded as responsible for the effects reported by Beecher [80, 81, 90]

Later in 1983, based on a random sample of 30 published randomized clinical trials, McDonald and Mazzuca [91] estimated the magnitude of the placebo effect. They reported a mean improvement of 9.9 percent and concluded that the placebo might have no effect because of results from this large statistical regression (i.e. regression to the mean). The latter, according to authors, may have accounted for the observed improvement after placebo treatment.

To answer the question of whether a placebo produces clinically significant effects, Hrobjartsson and Gøtzsche 2001 [80] conducted a meta-analysis that became an important contribution to the debate about the magnitude of the placebo effect. This meta-analysis included 114 clinical trials, across 40 clinical conditions, published prior to 1999. The study consisted of trials that included both placebo and non-treatment conditions. The purpose was to determine whether patients randomized to placebo under blind conditions had better outcomes when compared to subjects randomized to no treatment conditions. The authors found no reliable evidence of clinically relevant placebo effects. No significant effects

on objective or binary outcomes were found. The authors did state that placebo had small benefits in continuous subjective outcomes and for the treatment of pain.

However, the findings and the methodology of the above study have been debated and challenged by many authors. [22, 83-85, 89, 92] A problematic issue of the Hrobjartsson and Gøtzsche meta-analysis relates to the heterogeneity of the included studies. It has been reported that placebo does not work equivalently across different conditions. For example, conditions such as anxiety, pain, and involvement of the autonomic nervous system are associated with a favorable placebo response.[93] In contrast, chronic degenerative diseases or hyperacute illnesses (i.e. heart attack) are expected to respond poorly to placebo.[93] Thus, authors [85] propose that a better approach to determine the effects of placebo would be to analyze the trials according to their amenability to the placebo effect instead of considering the heterogeneity of disorders as included in the Hrobjartsson and Gøtzsche meta-analysis.

More importantly, authors have pointed out that the clinical methodology used by Hrobjartsson and Gøtzsche, 2001[80] was not well designed to detect placebo effects. Randomized clinical trials are limited for detecting the placebo effect. Rather, this design is useful for demonstrating that a treatment is specific for a disorder, and also to estimate the specific treatment effects.[37, 85] In the standard disclosure for a randomized clinical trial, patients are told that they will receive either a real intervention or a placebo treatment. This scenario creates a level of uncertainty among patients about what they actually received (i.e. active treatment

or placebo).[94] Thus, under this informational context in which the patient is unaware of the treatment, or if the placebo is indistinguishable from the treatment, it is unlikely that associated positive expectations, a factor consistently associated with placebo analgesia, [12, 29, 32, 48, 50, 58, 95] could be triggered. Accordingly, the evidence from meta-analyses suggests that when a placebo is included as a mere control or comparison, in the context of standard disclosure in double-blind placebo-controlled trials, the magnitude of placebo analgesia is low, as indicated by an effect size of 0.15-0.27 (Cohen's d or pooled standardized mean difference).[80-82] An exception to this notion is a recent meta-analysis investigating the placebo effect in osteoarthritis clinical trials, in which the effect size for the placebo was d= 0.51 when compared to a control/non treatment group (d= 0.03). [86]

To clarify the methodological debate about the magnitude of the placebo effect, Walpond et al. 2005 [85] reanalyzed the study of Hrobjartsson and Gøtzsche 2001.[80] In this new meta-analysis, the authors analyzed the studies based on the conditions' amenability to a placebo treatment. The authors conclude that when a condition is amenable to placebo effect (e.g. insomnia, pain, depression), the placebo action was detected (i.e. Cohen d= 0.29 for continuous outcomes). In addition, when the disorder was amenable to the psychological aspects of a placebo, no significant differences were found between the active treatment and placebo treatment. In contrast, when the disorder was not amenable to placebo action (e.g. anemia, bacterial infection), the specific treatment (active) was superior to the placebo treatment (d= 0.65). This suggests that a placebo can

produce comparable effects to that produced by the active treatments, but only in amenable medical conditions or outcomes.[85] On the other hand, when the magnitude of placebo effect was calculated in studies evaluating the analgesic effects /mechanisms of placebo analgesia, the results differed from those calculated in randomized controlled trials. [22, 83, 84] For example, Vase et al[22] compared 23 clinical trials of pain management included in the meta-analysis of Hrobjartsson and Gøtzsche 2001[80] with 14 experimental studies evaluating placebo analgesia that included a no-treatment condition. The authors concluded that the mean effect size of the placebo in the clinical trials was 0.15 compared with 0.95 in the studies evaluating placebo analgesia (P= 0.003). In a reanalysis of the data originated from Hrobjartsson and Gøtzsche 2001,[80] the same authors concluded that the effect size for the experimental placebo mechanisms was d= -0.56, and the effect size for the analgesic trials not investigating the analgesic mechanisms (i.e. randomized controlled studies) was d= -0.19.[82] Thus, although the magnitude of the effect was reduced significantly when compared with the Vase et al[22] study, the effect size for the studies of placebo analgesic mechanisms was still nearly three times greater than the effect size observed in randomized controlled trials.

In agreement with the previous studies, authors of a new meta-analysis aimed at understanding the mechanisms of placebo analgesia pooled the effects of studies during the period of 2002- 2007 [84]. The authors found that the magnitude of the placebo analgesia in these placebo mechanism studies was about five times larger (d= 1.00) than placebo analgesia in placebo controlled studies (d= 0.15-0.27). In

studies investigating the mechanisms of placebo analgesia, distinct from the randomized clinical trials, the experiments are explicitly designed to assess the existence of the placebo effect and/or elucidate its mechanisms.[94] Such studies can be conducted using both healthy volunteers in experimental conditions and patients in clinical settings. In mechanistic studies, subjects are deceptively informed that they will receive a powerful painkiller, or a successful analgesic intervention, when in fact they are being administered a placebo. Thus, the uncertainty associated to the randomized clinical trials about being administered a real treatment is ruled out. In the same way, such expectation-inducing context is believed to more closely resemble clinical practice than the informational context provided to patients in randomized clinical trials .[22, 94]

In summary, there is a considerable variability and controversy regarding the magnitude of the placebo effect. The variability may be explained by the environmental and psychosocial determinants of placebo response/effects (e.g. conditioning, suggestions, and therapeutic alliance) as well as the conditions being investigated. Additionally, since the placebo effect is prone to bias (e.g. report bias, response bias, publication bias) [87] this susceptibility may also account for the variability in the magnitude presented in the literature. With some degree of controversy, it seems that placebo could be powerful in situations and medical conditions where it would be expected to operate. Also, placebo effects appear to be larger in studies using placebo applications to study the mechanisms of placebo analgesia compared to placebo applications in clinical trials. However, the conflicting data related to the power of the placebo effect, and the informational

context hypothesis, in which a patient could produce greater placebo analgesia when she/he is deceptively informed compared to being informed that they will receive either a placebo or active treatment, certainly require further research.

2.8. THERAPEUTIC ALLIANCE

The placebo response is founded on interactions between the clinician, the treatment process, and the patient.[96] Placebo operates whenever patients and clinicians interact, especially in medical conditions amenable to this effect. Since these interactions provide meaning and modify patient expectations and beliefs, they likely play a critical role in placebo effects.[23]

The therapeutic alliance or the patient-practitioner relationship can be defined as the working rapport or positive social connection between the patient and the therapist.[97] Among the diverse therapeutic contextual factors, the therapeutic alliance represents a critical factor that is fundamental to the therapeutic process. The alliance between patient and therapist has been correlated with treatment adherence and outcomes in several disciplines including medicine, psychotherapy, and physical rehabilitation. [98-101]

The construct of alliance refers to the sense of collaboration, warmth and support between client and therapist.[102] Three essential components that contribute to this construct are agreement on treatment goals, agreement on interventions, and the development of an affective bond between patient and therapist.[103] Therefore, an optimal therapeutic alliance is achieved when patient and therapist share beliefs

with regard to the goals of the treatment and view the methods used to achieve these as efficacious and relevant.[104]

The therapeutic alliance is another significant part of the non-specific effects of any intervention that can influence the magnitude of treatment outcomes and the placebo response. This construct occurs in the context of a dynamic, reciprocal, emergent relationship.[105] When achieved in an effective manner, the therapeutic alliance becomes a source of motivation, encouragement, and reassurance as well as an opportunity for revision of expectations of both therapist and patient. Therefore, an effective therapeutic alliance can lead to therapeutic change for the patient. In this interaction, the care-provider's attitude is important. For example, Thomas[106] evaluated the impact of physicians' positive attitudes on patient outcomes. He found that physician's advice to patients was more effective than the administration of a placebo prescription medication. In addition, a therapeutic relationship is considered to be an important factor in the management of chronic conditions.[105] Since chronic conditions demand considerable commitment by patients for implementing treatment regimes, a strong alliance between the care provider and patient is essential to achieve the patient compliance.

In therapies, including physiotherapy, the therapist and the patient bring to the therapeutic encounter a series of psychological variables such as cognition, expectancy, suggestion, communication, personality, and the introduction of trust and confidence. The interaction of these attributes can activate psychophysiological responses to generate the placebo effect in patients.[23] Physical rehabilitation disciplines, including physiotherapy, typically exhibit high

levels of patient-clinician interaction. Because of the nature of therapeutic interventions (e.g. touch, care, attention), physiotherapists have an opportunity to build quality relationships with their patients. Since the placebo effect is directly associated with the degree and quality of such interaction, the therapist could be a major contributor to the placebo response in physiotherapy.[107]

Some mechanisms have been proposed to explain the positive effects of the therapeutic alliance on treatment outcomes. For example, it has been shown that better clinician-patient interaction translates into a better treatment adherence.[98-101] More recently, evidence has shed light on the neurobiology of the clinician-patient relationship and the mechanisms of how appropriate words from the clinician can induce meaningful changes in neural activity leading to the activation of the endogenous opioid system, biological changes and improved outcomes.[27, 29, 33, 46] All of these studies taken together lead to a neurobiological understanding of the events occurring in the brain during the interaction between therapist and his/her patient.

Emerging evidence indicates that the degree and quality of the interaction between clinician and patient is important because it influences not only the magnitude of the active treatment but also the degree of the placebo effect. [27, 41, 61-63] For example, it has been shown that when the clinician-patient relationship is absent, the magnitude of the analgesic response is affected.[41, 61-63] Elimination of the therapeutic alliance negatively influences pain outcomes, possibly due to a reduced activation of opioid mechanisms in patients in the absence of the doctor or nurse during the clinical procedure.[49]

To further support the impact of therapeutic alliance on clinical outcomes, authors of a recent study [27] confirmed that the clinician-patient relationship was the most potent component of non-specific effects in the management of patients with irritable bowel syndrome. In this study, the magnitude of the effect for an augmented interaction (i.e. 45 minutes' duration including supportive, warm, active listening behaviors) between the therapist and the patient was not only statistically but also clinically significant for pain, symptom severity and quality of life outcomes compared with a limited interaction (i.e. 5 minutes) and the natural history of the condition (waiting list control). These results indicate that such factors as warmth, empathy, duration of interaction, and the communication of positive expectations might indeed significantly affect clinical outcomes.

The therapeutic alliance has been a matter of research in psychotherapy and medicine for many years. For example, the contribution of this construct to therapeutic outcomes, [85, 108, 109] as well as its predictive power [110] has been determined for psychotherapy interventions. In addition, aspects of the therapeutic alliance have been under analysis to establish the factors common across domains of psychotherapy.[111] Examples of common factors implicit to all treatment scenarios include the therapeutic alliance, therapist and client characteristics. [51, 109, 112] Evidence from systematic reviews and meta-analyses of effectiveness of interventions have confirmed that common factors account for approximately 70% of the variance in positive outcomes of psychotherapy interventions.[109] Thus, it appears that, in psychotherapy, the elements of therapeutic change lie in the

therapeutic interaction (i.e. non-specific factors) rather than the specific ingredients of the interventions.[109]

In medicine, a recent body of literature has shed light on the nonspecific effects of the doctor-patient relationship and communication styles on the outcome of treatment.[113-115] In some studies, the patients' perceived differences in treatment responsiveness are likely related to the physician's interpersonal skills rather than the appropriateness of the treatment technique. For example, patients who felt that the physician did not care about their welfare held their physician responsible for a negative outcome in what they perceived was an inadequate treatment.[114, 115] In contrast, therapeutic alliance has been largely overlooked in physiotherapy research. Additionally, the meaning of the therapeutic alliance or the therapeutic encounter has not attracted the attention needed to determine its relevance, or lack thereof, in the placebo response or its impact on treatment outcomes. Although therapeutic alliance has been shown to produce therapeutic benefits in some areas such as medicine and psychotherapy, there is little empirical support for this notion in physiotherapy. A recent systematic review pointed out that in physical rehabilitation, a consistent pattern of positive therapeutic alliance correlated with improved pain, disability and treatment satisfaction.[98] However, an estimate of the magnitude of association is still unknown. In addition, experimental manipulation of this construct is still needed for physiotherapy interventions in patients with painful musculoskeletal conditions to confirm a causal effect. Since factors common across interventions such as therapeutic relationship, expectations, and personal characteristics of patients are intrinsically related with the placebo

response, how these factors affect treatment outcomes and facilitate positive therapeutic change in physiotherapy warrant further study.

2.9. PLACEBO PREDICTORS

Despite some consensus on the physiologic mechanisms underlying the analgesic placebo effect, there is less agreement on the predictors of the placebo analgesia response. Analysis of the effectiveness of the placebo effect and placebo analgesia is enriched when the prognostic value of placebo determinants is taken into account.[116] Moreover, predicting the probability of an individual reacting to placebo in physiotherapy could have major implications for increasing the design and efficacy of clinical trials. A challenge is to identify the factors that could influence the placebo or the therapeutic contextual response in patients suffering from chronic musculoskeletal pain, especially chronic low back pain.

Although gender differences may contribute to explain the variability in the magnitude of placebo response,[117] this issue has often been overlooked when discussing and reporting results. The current evidence about the role of gender as a contributor to placebo analgesia is represented by only a limited number of clinical studies.[118, 119] For example, no gender differences in placebo analgesia have been reported in acute clinical pain.[118, 119] It is worth mentioning that no data exist for the prognostic value of gender on placebo response in chronic painful conditions. Although a significant placebo effect has been reported among older patients with depression,[120] and Parkinson's disease,[44] the role of age as a contributor to placebo response in musculoskeletal pain is unclear.

In addition, the predictive role of psychosocial variables (i.e. therapeutic alliance, expectancy) or clinical presentation (i.e. pain intensity, disability) for placebo analgesia in chronic low back pain is unknown. While some evidence exists regarding the importance of some specific attributes, such as expectancies of recovery as a predictor of clinical outcomes in low back pain patients receiving physiotherapy [59, 121] little is known about whether or not this factor contributes to placebo analgesia under the same clinical conditions. Contextual factors such as therapeutic alliance have been reported as positively associated with treatment outcome in psychotherapy and medicine. [109, 122-124] However, the characteristics of the patient population and interventions from these disciplines differ from physiotherapy. Therefore, it is of great importance to determine the role of therapeutic alliance as a potential predictor of treatment outcome as well as a predictor of the placebo response in physiotherapy.

Despite some direct associations reported between the baseline level of pain intensity and the magnitude of the placebo response in osteoarthritis,[37] data about the contribution of this factor as a determinant for the placebo physiotherapy response in patients with chronic low back pain is still absent. Disability is also a common feature of chronic low back pain. The extent to which this variable can influence the placebo response is not well understood. For example, to date no association has been confirmed between levels of disability and placebo physiotherapy analgesia in patients with chronic pain. Considering the high prevalence of disability in patients with chronic low back, it seems important to

determine whether or not this factor influences the placebo response in patients receiving physiotherapy interventions.

2.10. THERAPEUTIC CONTEXTUAL FACTORS IN PHYSIOTHERAPY: CLINICAL IMPLICATIONS

For a more integrated, effective and client-centered approach, physiotherapy demands a comprehensive analysis of all factors that potentially could influence its clinical efficacy.[111] This is of utmost importance, especially in clinical conditions such as chronic low back pain where the effects of specific ingredients of physiotherapy interventions have been proven to be of limited action.[3, 11, 125] Because it is inherently related to the biomedical model, much of the current information in physiotherapy deals with the analysis and study of the specific effects related to different interventions. Although routinely present in clinical practice, researchers who have attempted to build physiotherapy's 'evidence base' have consistently ignored the potential contribution of the placebo process or the nonspecific factors in treatment responsiveness. Therefore, information about the influence of the therapeutic contextual factors (e.g. alliance, expectations) in treatment outcomes in physiotherapy, and their clinical utility has been seldom discussed. Addressing the non-specific factors may contribute to obtaining better outcomes in chronic pain trials.[125] Therapies, including physiotherapy, are rich in cues and rituals involving sensory variables (i.e. visual, auditory, touch).[126] Examples of visual environmental cues include the nature of the therapist's uniform and therapeutic equipment. Similarly, auditory cues are be represented by

verbal suggestions and the confidence displayed by the clinician. All of these stimuli may act as powerful symbolic agents in alleviating pain. In addition, these features build a therapeutic encounter characterized by a strong patient-therapist alliance or interaction. Not surprisingly, a good therapeutic alliance often results in better rehabilitation outcomes, [65, 98] and patient satisfaction.[127] Thus, when conducted by enthusiastic therapists, the success rate of the placebo response has been found to increase by as much as 50%.[128] However, despite its potential as a placebo mediator, the patient-therapist alliance has been largely overlooked in physiotherapy placebo research. As with many areas of health, physiotherapy and particularly the application of electrophysical agents are likely to be prone to the influence of the placebo effect. On the basis of the influence of the psychosocial context affecting treatment responsiveness, it is plausible that the use of new, expensive and technologically impressive equipment such as ultrasound, laser and electro stimulators along with the use of adequate and persuasive verbal suggestions during physiotherapy treatments could build an adequate psychosocial context to trigger certain responses. This may include positive expectations and motivation for pain relief that could be beyond the physiological effects of the specific therapeutic interventions. In this regard, although expectations may modify pain perception, [29, 32, 33] experimental manipulation of this construct needs to be incorporated when studying physiotherapy interventions for musculoskeletal painful conditions to determine its relevance in clinical outcomes.

Although the placebo effect has attracted the interest of the scientific and clinical community, this phenomenon continues to be a relatively unexplored area of study in physiotherapy. Thus, the effects of therapeutic contextual factors when delivering physiotherapy treatments have not been fully explored in a quantitative manner. This is probably more noticeable in popular electroanalgesia modalities such as IFC, where little is known about how this phenomenon operates. For example, a literature search of PEDro, MEDLINE, Scopus, and Embase (1966–2011), found only two [36, 58] experimental studies (no clinical study was found) investigating the direct measurement of the placebo effect of IFC by comparing placebo IFC with no intervention (e.g. control), instead of using the difference between the placebo condition and active IFC treatment, to assess the efficacy of the active treatment of interest. Results from these studies revealed conflicting results. Roche et al. 2002, [58] showed that placebo IFC was able to modulate experimentally-induced ischemic pain compared to a control condition. In another study dealing with a mechanically-induced experimental pain, placebo application was not superior to a control in decreasing muscle pain sensitivity.[36] The discrepancy observed in these results might be explained by differences in treatment protocol and the type of experimental pain used in both studies. On the basis of these findings, the impact of therapeutic contextual factors in physiotherapy remains unclear and further research is needed. Special effort must be directed at its effects on chronic pain where this issue has not been thoroughly analyzed nor discussed, but where placebo effects are anticipated.

Despite compelling evidence about the effects of placebo on treatment responsiveness in various health disciplines, very little is known about the role of the placebo effect as a pain modulator in physiotherapy interventions. Of particular interest is the need to determine the prognostic factors associated with the placebo effect, especially information regarding the role of expectancies and the therapeutic alliance in physiotherapy interventions for chronic low back pain, which has not been not fully assessed. In addition, the association between the placebo response and patient characteristics such as pain intensity, level of disability, and gender needs to be determined in patients with chronic low back pain receiving physiotherapy.

Placebo may well have a real therapeutic effect, with implications in the everyday clinical setting for physiotherapists.

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CHAPTER 3

EFFECTIVENESS OF INTERFERENTIAL CURRENT THERAPY IN THE MANAGEMENT OF MUSCULOSKELETAL PAIN: SYSTEMATIC REVIEW AND META-ANALYSIS

Background. Interferential current (IFC) is a common electrotherapeutic modality used to treat pain. Although IFC is widely used, the available information regarding its clinical efficacy is debatable.

Purpose. The aim of this systematic review and meta-analysis was to analyze the available information regarding the efficacy of IFC in the management of musculoskeletal pain.

Data Sources. Randomized controlled trials were obtained through a computerized search of bibliographic databases (ie, CINAHL, Cochrane Library, EMBASE, MEDLINE, PEDro, Scopus, and Web of Science) from 1950 to February 8, 2010.

Data Extraction. Two independent reviewers screened the abstracts found in the databases. Methodological quality was assessed using a compilation of items included in different scales related to rehabilitation research. The mean difference, with 95% confidence interval, was used to quantify the pooled effect. A chi-square test for heterogeneity was performed.

Data Synthesis. A total of 2,235 articles were found. Twenty studies fulfilled the inclusion criteria. Seven articles assessed the use of IFC on joint pain; 9 articles evaluated the use of IFC on muscle pain; 3 articles evaluated its use on soft tissue shoulder pain; and 1 article examined its use on postoperative pain. Three of the 20 studies were considered to be of high methodological quality, 14 studies were considered to be of moderate methodological quality,

and 3 studies were considered to be of poor methodological quality. Fourteen studies were included in the meta-analysis. Conclusion. Interferential current as a supplement to another intervention seems to be more effective for reducing pain than a control treatment at discharge and more effective than a placebo treatment at the 3-month follow-up. However, it is unknown whether the analgesic effect of IFC is superior to that of the concomitant interventions. Interferential current alone was not significantly better than placebo or other therapy at discharge or follow-up. Results must be considered with caution due to the low number of studies that used IFC alone. In addition, the heterogeneity across studies and methodological limitations prevent conclusive statements regarding analgesic efficacy

3.1. INTRODUCTION

Successful management of musculoskeletal pain is a major challenge in clinical practice. One of the electrotherapeutic techniques used for treating musculoskeletal pain is interferential current therapy (IFC). The results of questionnaire surveys in England,[1] Canada [2] and Australia [3, 4] have shown that IFC is widely used by diverse clinicians throughout the world.

IFC is the application of alternating medium-frequency current (4000 Hz) amplitude modulated at low frequency (0 to 250 Hz).[5-7] A claimed advantage of IFC over low-frequency currents is its capacity to diminish the impedance offered by the skin. [6] Another advantage speculated for IFC is its ability to generate an amplitude modulated frequency (AMF) parameter, which is a low frequency current generated deep within the treatment area. [6, 8-10] Several theoretical physiological mechanisms such as the "gate control" theory, [11] increased circulation, descending pain suppression, block of nerve conduction and placebo have been proposed in the literature to support the analgesic effects of IFC. [5, 8, 12]

Despite its widespread use, the information about IFC is limited. A review of the literature reveals incomplete and controversial documentation regarding the scientific support of IFC in the management of musculoskeletal pain. For example, a systematic review about the use of electrotherapy for neck disorders [13] excluded the analysis of IFC. Moreover, much of the IFC information is not written in English [10, 14-22] and most papers appear to be based on case reports,[23-25]

clinical studies not including a randomization process,[26, 27] letters to the editor [28, 29], clinical notes,[30] or experimental settings,[31-37] descriptive studies, [8, 12, 38, 39] or experience in the field [40, 41] instead of methodologically qualified studies.

Thus, the objective of this systematic review and meta- analysis was to determine the analgesic effectiveness of IFC when compared with control, placebo or other treatment modalities for decreasing pain in patients with musculoskeletal painful conditions.

3.2. METHODS

3.2.1. SEARCH STRATEGY

Relevant studies of IFC in musculoskeletal pain management from 1950 to February 8 2010 , were obtained through an extensive computerized search of the following bibliographic databases: MEDLINE (1950 through week 4 2010), Embase (1988 through week 5 2010 2), CINAHL(1970 through February 08 th 2010), Scopus (1970 through February 08th 2010), Cochrane Library (1991 through first quarter 2010), ISI Web of Science (1970 through February 08th 2010), PEDro Physiotherapy Evidence Database (1970 through February 08th 2010). The key words "interferential", "interferential therapy", "interferential current", "musculoskeletal pain", "electrotherapy", "electroanalgesia", "muscle pain", "low back pain", "shoulder pain", "hip pain", "knee pain", "neck pain", "osteoarthritis pain", and "joint pain" were used in the search, including

combinations of these words. For details regarding the search terms and combinations see eAppendix 1 (available at ptjournal.apta.org). The literature search procedure was complemented by manually searching the bibliographies of the identified papers for key authors and journals.

3.2.2. STUDY SELECTION AND INCLUSION/EXCLUSION CRITERIA

Studies meeting the following criteria were considered for inclusion: (1) randomized controlled trials (RCTs) from journal publications in the English language (because the clinical application of IFC is often based on its coadjutant effect, studies in which IFC was used as a co-intervention also were included); (2) studies of male and female humans between 18 and 80 years of age; (3) studies of subjects clinically diagnosed with a painful musculoskeletal condition such as muscle (e.g. low back pain, neck pain), soft tissue (tendinosis/tendinitis), or joint disorders (e.g. osteoarthritis); (4) regarding the type of interventions, all randomized comparisons of isolated or coadjutant IFC applications versus placebo, control, another physical therapy or another type of intervention; and (5) studies in which the outcome of interest was pain, as measured by the use of the visual analogue scale (VAS) or numerical pain rating scale (NRS). Exclusion criteria for this study were: (1) studies based on animal data, (2) studies published in languages other than English, and (3) studies including subjects that were healthy in experimental settings.

3.2.3. DATA EXTRACTION AND QUALITY ASSESSMENT

Two independent reviewers screened the abstracts of the publications found in the databases. The reviewers analyzed all papers initially selected by the abstract or title for the inclusion and exclusion criteria. Each criterion was graded on a yes/no basis. In case of discrepancies between reviewers regarding whether a particular paper met a criterion, the rating compared and the criterion forms were discussed until a consensus was reached.

A critical appraisal was conducted to determine the methodological quality of the final selected studies. We used 7 scales (i.e. Delphi List, PEDro, Maastricht, Maastricht- Amsterdam List, Bizzini, van Tulder and Jadad) commonly used in the physical therapy field to evaluate the methodological quality of the included studies, compiled in a set of 39 items.[42] These items are grouped into 5 categories: patient selection, blinding, intervention, outcomes, and statistics.

Based on a recent systematic review,[42] no one scale effectively determines the overall methodological quality of individual studies. For this reason, we used all of them in a compiled fashion.

The articles were evaluated using the critical appraisal sheet (eAppendix 2; available at ptjournal.apta.org). For each item listed on the critical appraisal sheet, a score of 1 was given when the item was included in the article, and a score of 0 was given when the item was not included or the information provided for the authors was not sufficient to make a clear statement.

In cases where the study did not consider a particular item, the item was marked as not applicable on the critical appraisal sheet. The scoring for each study was calculated dividing the number of items included by the number of applicable items. Finally, each study was graded as low, moderate or high methodological quality based on how many items from the critical appraisal were met. The cut-off was determined as follows; 0- 0.40 low methodological quality, 0.41- 0.70, moderate methodological quality, and 0.71- 1.0 high methodological quality. This criterion was determined a priori to the quality assessment. Similar criteria for cut-off have been used in correlational studies to determine reference values for quality of association/agreement. [43, 44]

The critical appraisal was independently completed by the two reviewers, and the results were compared. At this stage, the ICC was calculated using SPSS 17* in order to determine the agreement between the reviewers for article grading. Any discrepancies were settled through discussion.

3.2.4. DATA SYNTHESIS AND ANALYSIS

Studies investigating similar outcomes and interventions and those providing clear quantitative data were grouped, evaluated for heterogeneity and pooled, if possible. When combining outcome data was not possible, narrative, descriptive and qualitative summaries were completed. In the present study, a meta-analysis was performed to quantify the pooled effect of IFC alone or as an adjunct treatment when compared with placebo, control group or comparison intervention.

Because the pooled effect was based on the results of the VAS or NRS, the mean difference was used to quantify the pooled effect. Revman 5.0 Software† was used to summarize the effects (i.e. pooled mean differences) and construct the forest plots for all comparisons. For this analysis the 95% confidence interval was used. A test for heterogeneity was performed using a Chi-square test ($p<0.10$).[45] In the presence of clinical heterogeneity in the study population or intervention, the DerSimonian and Laird Random Effects Model of Pooling was used based on the assumption of the presence of inter-study variability to provide more conservative estimate of the true effect[45, 46]. If there was relative homogeneity, a fixed-effects model was used to pool data. [45]

3.3. RESULTS

A total of 2,235 articles were found in the database search. Of these, 154 were selected as potential studies of interest based on abstract review (Fig. 1). After full article review, only 20 studies were deemed to fulfill the initial selection criteria. [47-66] The kappa agreement between the reviewers in selecting articles after applying the inclusion and exclusion criteria was perfect at $k = 1.0$.

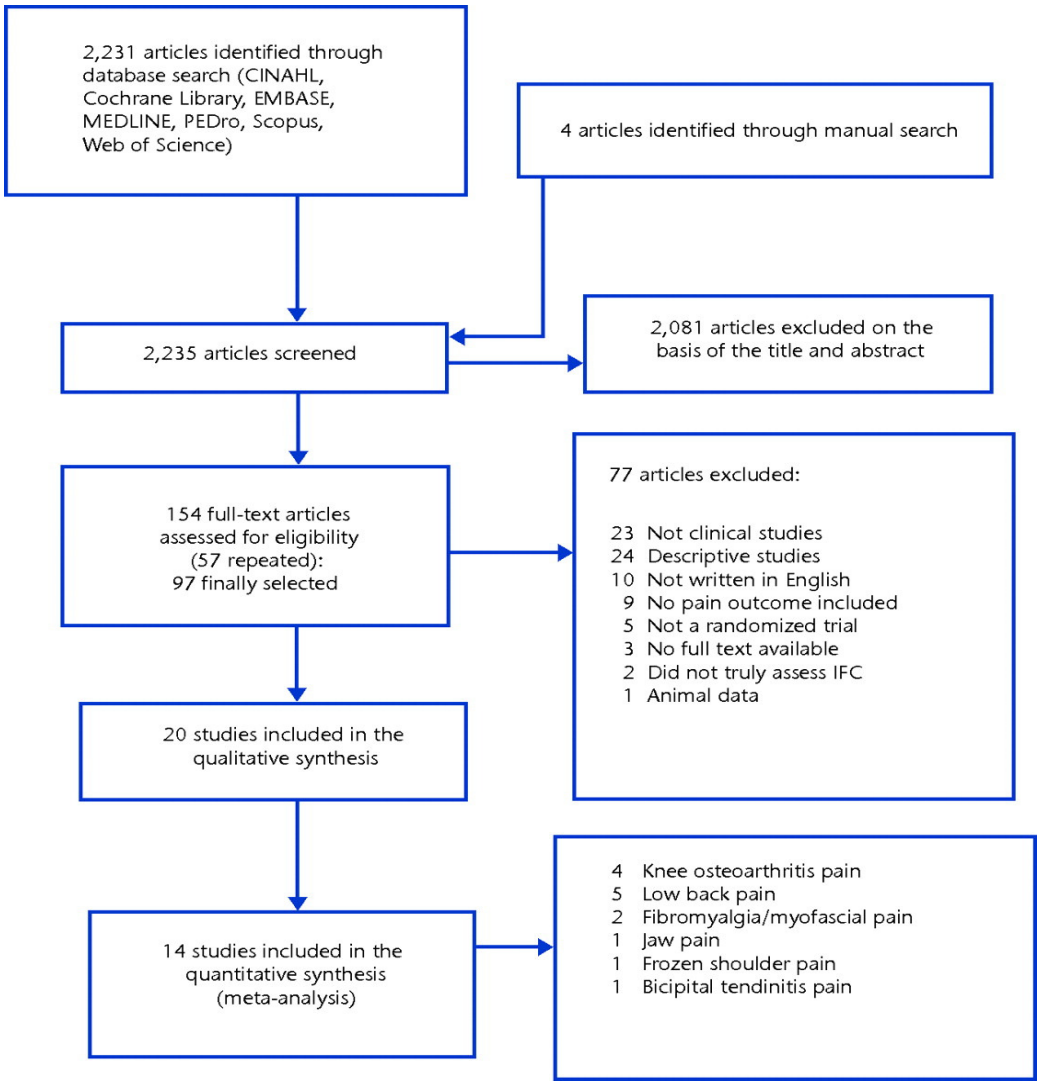

Figure 1. Study screening process. IFC= interferential current therapy.

Seventy-seven studies were rejected after applying the inclusion and exclusion criteria. The primary reasons for exclusion from the study were :(1) the use of subjects who were healthy in an experimental setting [31-37, 67-82], (2) descriptive studies in the form of case reports, dissertations, clinical notes,[8, 12, 23-25, 30, 38-41, 69,

[83-96], (3) studies not published in the English language, [10, 14-22] (4) the absence of pain outcomes [97-105], (5) randomized trial not used [26, 27, 106-108] (6) the use of a current different than IFC,[109, 110] (7) use of animal data:[111] and (8) the unavailability of the full text of the article.[112-114] At the end of the critical appraisal stage, there was an agreement of $k = 0.83$ between the two raters. This ICC value is considered as "excellent" agreement according to the approach described by McDowell.[115]

3.3.1. CHARACTERISTICS OF THE STUDIES

All 20 studies reviewed in detail were RCTs that examined the pain reducing effectiveness of IFC. These studies analyzed the effects of IFC for several diagnoses considered to be either acute or chronic painful conditions**.** Only 6 articles (30 %) [48, 54, 56, 57, 61, 63] examined the clinical analgesic effectiveness of IFC as a single therapeutic modality. The rest of the articles included the application of IFC as a co-intervention along with other therapeutic alternatives such as exercise,[47, 49, 53, 58-60, 62, 64, 65] shortwave diathermy,[51, 59] hot packs,[55, 60] ice,[58] myofascial release,[55] Neuromuscular Electrical Stimulation,[52] Infrared radiation , [51] and ultrasound . [50, 60, 62] Details of the studies' characteristics are shown in Table 1.

Table 1.
Characteristics of the Studies[a]

Study	Country	Condition	Sample	Study Arms	Outcomes	CoInterventions	Follow-up	Treatment	Results	Strengths/Weaknesses
Quirk et al,[59] 1985	England	Knee OA	38	1. Active IFC + exercises 2. Active SWD + exercises 3. Exercises	ROM, pain (VAS), exercise endurance, maximum knee girth	Exercises	3 and 6 mo	• 12 patients in the IFC + exercise group, 12 patients in the SWD + exercise group, and 14 patients in the exercise group • Frequency of 0–100 Hz for 10 min and 130 Hz for 5 min, 3 times a week for 4 wk	• Significant improvement in groups 1, 2 and 3 ($P<.02$, $P<.05$, $P<.03$, respectively) • No significant difference among groups	• Randomized • Confounders not controlled • Reliability and validity of outcomes not reported • Small sample size • No control/placebo group included • Poor description of intervention
Adedoyin et al,[47] 2002	Nigeria	Knee OA	30	1. Active IFC 2. Placebo IFC	Pain (VAS)	Exercises	None	• 15 patients in IFC group and 15 patients in the placebo group • IFC: 4 electrodes (2 placed lateromedially and 2 placed anteroposteriorly), frequency of 100 Hz for the first 15 min and 80 Hz for the next 5 min, intensity (appreciable sensation) • Both groups had treatments and mobilization exercise twice a week for 4 wk	• Significant difference between initial and final pain rating in both groups ($P<.01$) • Significance difference between 2 groups after treatment ($P<.01$). Pain rating was found to be significantly better in the active IFC group than in the placebo group.	• Randomized • Clinicians blinded • Good control of confounders • Good description of intervention • Small sample size • Validity of outcomes not reported
Adedoyin et al,[49] 2005	Nigeria	Knee OA	51, 5 were excluded from the analysis	1. IFC + exercise 2. TENS + exercise 3. Exercise alone	Functional disability (WOMAC), pain (10-point pain rating scale)	Exercises	None	• 15 patients in the TENS + exercise group, 16 patients in the IFC + exercise group, and 15 patients in the exercise only group • IFC: 2 electrodes (either side of the knee longitudinally), frequency of 80 Hz, continuous, intensity (strong tingling sensation), 20-min session, 2 sessions a week for 4 wk	• Significant time effect in WOMAC and pain scores ($P<.001$) • No significant difference between groups in WOMAC and pain scores ($P=.241$, $P=.813$) • All treatment protocols led to significant reductions in pain and improvement in function	• Randomized • Clinicians blinded • Sample size calculated *a priori* and adequate • Good description of intervention • Confounders not controlled • No control/placebo group included • Reliability of outcomes not reported
Defrin et al,[54] 2005	Israel	Knee OA	62	1. Active IFC noxious stimulus unadjusted 2. Active IFC noxious stimulus adjusted 3. Active IFC innocuous stimulus unadjusted 4. Active IFC innocuous stimulus adjusted 5. Placebo IFC 6. Control	Pain intensity (VAS), pain relief (0–100%), morning stiffness (10-cm line scale), active ROM (goniometer), electrically induced pain threshold (interferential current equipment)	None	None	• 11 patients in group 1, 11 patients in group 2, 12 patients in group 3, 11 patients in group 4, 9 patients in the placebo group, 8 patients in the control group • 2 electrodes (medial and lateral aspects of the knee): carrier current of 4,000 Hz, frequency between 30 and 60 Hz, intensity 30% above (noxious) or 30% below (innocuous) pain threshold, raise intensity (maintain sensation) for adjusted groups, 12 sessions every other day for 4 wk	• Significant improvement in groups 1 to 4 compared with the control group ($P<.001$) • Significantly larger decrease in noxious groups (1 and 2) for pain intensity ($P<.05$) and pain thresholds ($P<.01$) when compared with innocuous groups (3 and 4) • No significant difference between adjusted and unadjusted groups ($P=.47$)	• Randomized • Good description of intervention • Small sample size • Confounders not controlled • Reliability and validity of outcomes not reported • Control and placebo groups included

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Study	Country	Condition	Sample	Study Arms	Outcomes	Conterventions	Follow-up	Treatment	Results	Strengths/Weaknesses
Atamaz et al,[51] 2006	Turkey	Knee OA	85, 2 dropped out at discharge	1. Active IFC + IR + SWD 2. Intra-articular hyaluronan	Movement (ROM), pain (VAS), and function (SF-36, WOMAC, 15 min walking time)	IR and SWD	1, 3, 6, 9, and 12 mo	• 40 patients in the hyaluronan group (20 NaHA, 20 hylan) and 42 patients in the physical therapy group • Treatment applied 5 times a week for 3 wk with a series of IR, SWD, and interferential therapy	• Significant improvement in WOMAC, SF-36, and pain scores in both groups ($P<.05$) • Significant difference for pain at rest, pain on touch, and SF-36 in favor of physical therapy group at 1, 3, and 6 mo ($P<.05$) • Significant difference in WOMAC scores in favor of hyaluronan group ($P<.05$)	• Randomized • Clinicians blinded • Small sample size • No description of physical therapy interventions • Confounders not controlled • Reliability and validity of outcomes not reported • No control/placebo group included
Burch et al,[52] 2008	United States	Knee OA	116, 15 dropped out at discharge	1. IFC + NMES 2. Low-current intensity TENS	Pain and knee function (WOMAC), pain intensity (VAS), quality of life (VAS)	NMES	None	• 57 patients in the IFC + NMES group, 59 patients in the low-current TENS group • 15 min of true IFC (5 KHz with a beat sweep frequency of 1–150 Hz) followed by 20 min of NMES • 5 times a week for 8 wk	• IFC + NMES group reduced pain and increased function compared with low-current intensity TENS • The IFC + NMES group had a significantly greater decrease in overall pain VAS ($P=.038$)	• Multicenter RCT • Clinicians blinded • Adherence tested • Sample size calculated *a priori* and appropriate • No true control/placebo group included • Confounders well controlled • Adverse effects reported • Reliability of outcomes not reported
Werners et al,[53] 1999	Germany	Chronic LBP	152, 20 were lost at 3-month follow-up	1. Active IFC 2. Lumbar traction + massage	Disability (Oswestry Disability Index), pain (VAS)	None	3 mo	• 74 patients in the IFC group and 73 patients in the traction group • 2 electrodes (placed paravertebrally in pain area), frequency of 30–60 Hz, six 10-min sessions over 14–21 d	• Significant improvement in both groups ($P<.05$) • No significant difference between groups	• Randomized • Sample size calculated *a priori* and appropriate • Confounders not controlled • Reliability and validity of outcomes not reported • No control/placebo group included
Hurley et al,[57] 2001	Northern Ireland	Acute LBP	60, 12 dropped out at 3-mo follow-up	1. Active IFC painful area + The Back Book 2. Active IFC spinal nerve + The Back Book 3. Control (The Back Book)	Pain (PRI), disability (RMDQ), generic health status (EQ-5D)	None	3 mo	• 18 patients in the painful area group, 22 patients in the spinal nerve group, and 20 patients in the control group • 2 electrodes, carrier frequency of 3,850 Hz, frequency of 140 Hz, 30 min • 2–3 treatment sessions weekly until discharge	• Significant improvement in pain severity, disability and health status for all groups at discharge ($P<.05$) and at follow-up ($P<.01$) • Significantly greater RMDQ score in spinal nerve group ($P=.042$)	• Randomized • Good description of treatment • Small sample size • Confounders not controlled • Clinical significance reported • Reliability and validity of outcomes not reported
Hurley et al,[56] 2004	Northern Ireland	Acute LBP	240, 82 lost at 12-mo follow-up	1. Active IFC 2. Manipulative therapy 3. IFC + manipulative therapy	Functional disability (RMDQ), pain (VAS, MPQ), quality of life (EQ-5D, SF-36), LBP (recurrence, work absenteeism, analgesic consumption, additional health care)	None	6 and 12 mo	• 52 patients in the MT group, 55 patients in the IFC group, and 51 patients in the MT + IFC group • 2 electrodes on spinal nerve root placement, carrier frequency of 3,850 Hz, frequency of 140 Hz, 30 min • 4 to 10 sessions over a period of 8 wk	• Significant improvement in all groups at discharge, 6 mo, and 12 mo ($P<.05$) • No significant difference between groups ($P>.05$)	• Randomized • Assessors blinded • Good description of treatment • Sample size calculated *a priori* and appropriate • Adverse effects reported • Clinical significance reported • No control/placebo group included • Reliability and validity of outcomes reported

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Study	Country	Condition	Sample	Study Arms	Outcomes	Cointerventions	Follow-up	Treatment	Results	Strengths/Weaknesses
Lau et al,[66] 2008	Hong Kong	Acute LBP	110, 6 lost at 6-mo follow-up	1. IFC + medication + education + mobility and walking training 2. Walking training (control group)	Pain (NRS), satisfaction (Numeric Global Rating of Change Scale), disability (RMDQ)	Education, medication, mobility, and walking training	1, 3, and 6 mo	• 55 patients in the physical therapy group and 55 patients in the control group • 4 suction-type electrodes applied around the painful area, sweep frequency 70–130 Hz, intensity just below the pain threshold, 15 min • 1 or 2 sessions over a 24-hr period	• Significant decrease in pain (α=.025) and increase in satisfaction at discharge from the accident and emergency department • No significant difference between groups (α=.025) at 1, 3, and 6 mo follow-ups	• Randomized • Allocation adequate • Assessors blinded • Sample size calculated *a priori* • Intention-to-treat analysis included • High follow-up adherence • No placebo group included • Homogeneity of subjects uncertain
Adedoyin et al,[48] 2005	Nigeria	Chronic LBP	39	1. Active IFC swing pattern 1 integral 1 2. Active IFC swing pattern 6 integral 6 3. Active IFC swing pattern 6 wedge 6	Pain intensity (Verbal Semantic Differential Scale)	None	None	• 13 patients in the 1/1 group, 13 patients in the 6/6 group, 13 patients in the 6 wedge 6 groups • 2 electrodes (spinal nerve root correspondence to painful area), frequency of 100 Hz for burst group, sweep set between 50 and 100 Hz for the 6/6 and the 6 wedge 6 groups, carrier frequency of 4,000 Hz in the channel, channel 2 set to fluctuate between 4,050 and 4,100 Hz • 2 treatment sessions daily for 2 times a week for 3 wk	• Significant decrease in pain over time (P<.001) • No significant effect between groups (P=.063)	• Randomized • Patients blinded • Good description of treatments • Small sample size • No control group • Confounders not controlled • Validity and reliability of outcomes not reported
Zambito et al,[65] 2006	Italy	Chronic LBP	120	1. Active IFC 2. Active horizontal therapy 3. Sham horizontal therapy	Functional questionnaire (Backill), pain (VAS), analgesic consumption	Exercise, analgesic medication	1 and 3 mo	• 45 patients in the active IFC group, 45 patients in the active horizontal therapy group, and 30 patients in the sham horizontal therapy group • 4 electrodes on a standard dermatomal pattern; frequency of 200 Hz, 10 min • 5 sessions weekly for 2 wk	• At discharge, significant and similar improvement in both the VAS and Backill score was reported in all 3 groups (P<.05) • The function and VAS scores continued to improve at 3 mo in the active groups compared with control (placebo) group (P<.01)	• Randomized • Sample size calculated *a priori* and adequate • Double blind approach • Validity and reliability of outcomes not reported • Moderate description of treatment
Zambito et al,[64] 2007	Italy	Chronic LBP	115	1. Active IFC 2. Active horizontal therapy 3. Sham horizontal therapy	Functional questionnaire (Backill), pain (VAS), analgesic consumption	Exercise, analgesic medication	1 and 3 mo	• 35 patients in the active IFC group, 35 patients in the active horizontal therapy group, and 35 patients in the sham horizontal therapy group • 4 electrodes on a standard dermatomal pattern, frequency of 200 Hz, 30 min • 5 sessions weekly for 2 wk	• At discharge, significant and similar improvement in both the VAS and Backill score was reported in the 3 groups (P<.01) • The function and pain scores continued to improve in the 2 active groups at weeks 6 and 14 compared with the control (placebo) group (P<.01)	• Randomized • Sample size calculated *a priori* and adequate • Double blind approach • Validity and reliability of outcomes not reported • Moderate description of treatment

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Study	Country	Condition	Sample	Study Arms	Outcomes	Cointerventions	Follow-up	Treatment	Results	Strengths/Weaknesses
van der Heijden et al,[62] 1999	The Netherlands	Unspecified shoulder soft tissue condition	180, 1 dropped out at 12-mo follow-up	1. Active IFC + active US 2. No IFC + No US 3. Sham IFC + Sham US	Recovery, functional status (SDQ), chief complaint, pain (VAS), clinical status, ROM (goniometer)	Education and exercises	3, 6, 9, and 12 mo	• 34 patients in the active ET + active US group, 39 patients in the active ET + dummy US group, 39 patients in the dummy ET + active US group, 33 patients in the dummy ET + dummy US group, 35 patients in the no adjuvant group • 2 electrodes (1 in deltoid muscle region, 1 over homolateral erector trunci muscles), carrier frequency of 4,000 Hz, frequency of 60–100 Hz, intensity of electric paresthesia, 15 min, 12 sessions over 12 wk	• No significant difference between groups up to 12 mo follow-up (95% CI)	• Randomized • Patients and assessors blinded • Clinical significance reported • Sample size calculated *a priori* and adequate • Good description of treatment method
Taskaynatan et al,[60] 2007	Turkey	Bicipital tendinitis	47	1. IFC + US + hot packs + exercises 2. Steroid iopthoresis + US + hot packs + exercises	Pain (VAS), ROM (goniometer), patient satisfaction (NRS), disability (function section of the Pennsylvania Shoulder Scale)	US+ hot packs + exercises	1 mo	• 21 patients in the IFC + US + hot packs + exercises group, 26 patients in the steroid iontophoresis + US + hot packs + exercises group • AMF frequency 0–100 Hz, 15 min, 15 sessions	• Statistical significant improvement at discharge and 1-mo follow-ups in the steroid iontophoresis group ($P<.05$) • Less dramatic improvement was reported for the IFC group at discharge and 1-mo follow-up ($P<.05$)	• Randomized • Assessors blinded • Poor description of interventions • Validity and reliability of outcomes not reported • Adverse effects reported • No dropouts reported
Cheing et al,[53] 2008	Hong Kong	Frozen shoulder	74, 4 dropped out at 8-mo follow-up	1. Active IFC 2. Active electro-acupuncture 3. Control	Shoulder function (Constant Murley Assessment Score), pain (VAS)	Exercise	1, 3, and 6 mo	• 24 patients in the IFC group, 25 patients in the electroacupuncture group, 25 patients in the control group • 4 suction-type electrodes around the shoulder in a coplanar arrangement, intensity just below the pain threshold, AMF swept frequency 80–120 Hz, 20 min • 10 sessions over 4 wk	• Both active groups showed a significant improvement at discharge and 6-mo follow-up for function and pain scores ($P<.001$) • No significant change was found in the control group, and no significant difference was found between the 2 active groups ($P>.05$)	• Randomized • Patients and assessors blinded • Reliability and validity of outcomes moderately reported • Good description of treatment protocols

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Study	Country	Condition	Sample	Study Arms	Outcomes	Conterventions	Follow-up	Treatment	Results	Strengths/Weaknesses
Hou et al,[55] 2002	Taiwan	Cervical myofascial pain	71	1. Hot pack, active ROM group 2. Hot pack, active ROM, ischemic compression group 3. Hot pack, active ROM, ischemic compression, TENS group 4. Hot pack, active ROM, stretch group 5. Hot pack, active ROM, stretch, TENS group 6. Hot pack, active ROM, IFC, myofascial release group	Index of change in pain threshold (algometer), pain tolerance (algometer), pain (VAS), and cervical ROM (goniometer)	Hot pack, active ROM, myofascial release	None	• 21 patients in the hot pack, active ROM group (B1); 13 patients in the hot pack, active ROM, ischemic compression group (B2); 9 patients in the hot pack, active ROM, compression, TENS group (B3); 10 patients in the hot pack, active ROM, stretch group (B4); 9 patients in the hot pack, active ROM, stretch, TENS group (B5); 9 patients in the hot pack, active ROM, IFC, myofascial release group (B6) • 4 electrodes; frequency of 100 Hz, carrier frequencies of 4,000 Hz and 4,100 Hz, 20 min	• Significant improvement in all groups ($P<.05$) • Groups B2, B3, B4, B5, and B6 had significantly larger improvement than group B1 ($P<.05$) • Groups B3, B5, and B6 had significantly larger improvement than group B2 ($P<.05$) • Group B6 had significantly larger improvement than group B4 ($P<.05$) • No significant difference among groups B3, B5, and B6	• Randomized • Good description of treatment • Sample size calculated *a priori* • No control/placebo group included • Reliability and validity of outcomes not reported
Almeida et al,[50] 2003	Brazil	Fibromyalgia	40, 23 dropped out	1. Active IFC + US 2. Placebo IFC + US	Pain (body map, VAS), tender points, (tender point threshold), polysomnography, sleep questionnaire	US	None	• 9 patients in the US + IFC group and 8 patients in the sham treatment group • Carrier frequency of 4,000 Hz, frequency of 100 Hz, intensity in the tactile sensation, 12 sessions for 4 wk	• Significant reduction in pain intensity and painful areas in the combined therapy group ($P<.001$) • No significant difference in sham treatment group	• Randomized • Investigator blinded • Small sample size • Very low adherence (missing data 57.5%) • Reliability and validity of measurement not reported
Taylor et al,[61] 1987	United States	Chronic jaw pain	40	1. Active IFC 2. Placebo IFC	Jaw pain (VAS), function (maximum vertical jaw opening)	None	None	• 20 patients in the IFC group and 20 patients in the placebo group • 4 electrodes (extraorally 1–1.5 cm in front of the tragus of ear), frequency of 90–100 Hz for 15 min and 40–90 Hz for 5 min, intensity (comfortable but not too strong), 3 treatments (24–72 hr between treatments)	• Significant improvement in both groups for pain and maximal vertical jaw opening • No significant difference between groups ($P<.05$)	• Randomization used • Patients blinded • Confounders not controlled • Reliability and validity of outcomes not reported • Small sample size • Good description of treatment
Jarit et al,[58] 2003	United States	Postoperative knee pain	87	1. Active IFC 2. Placebo IFC	Postoperative edema, pain (VAS), pain medication, ROM (goniometer)	Ice, exercises	None	• 28 patients in the ACL group (14 IFC and 14 placebo IFC), 34 patients in the meniscectomy group (17 IFC and 17 placebo IFC), 25 patients in the chondroplasty group (15 IFC and 10 placebo IFC) • 4 electrodes, frequency of 5–10 Hz in first 14 min, 80–150 Hz in second 14 min, 3 times daily for 7–9 wk	• Significantly less pain and greater ROM for the active IFC in all groups at all time points ($P<.05$)	• Randomized • Assessor blinded • Good description of treatment • Reliability and validity of outcomes not reported

[a] OA=osteoarthritis, IFC=interferential current therapy, SWD=shortwave diathermy, ROM=range of movement, VAS=visual analog scale, TENS=transcutaneous electrical nerve stimulation, WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index, IR=infrared radiation, SF-36=36-Item Short-Form Health Survey questionnaire, NMES=neuromuscular electrical stimulation, PRI=Pain Rating Index, RMDQ=Roland-Morris Disability Questionnaire, EQ-5D=EuroQol EQ-5D questionnaire, MT=manual therapy, MPQ=McGill Pain questionnaire, LBP=low back pain, US=ultrasound, SDQ=Shoulder Disability Questionnaire, ET=electrotherapy, CI=confidence interval, NRS=numeric rating scale, AMF=amplitude-modulated frequency, ACL=anterior cruciate ligament.

3.3.2. METHODOLOGICAL QUALITY OF THE STUDIES

The results of the critical appraisal for the selected studies are presented in Table 2. Three out 20 studies were considered of high methodological quality, 14 studies were considered to be of moderate quality, and 3 studies were considered to be of poor quality. Even though the quality of most of the studies was rated as acceptable (17 studies were rated as being of moderate or high quality), there are some points regarding quality that need to be highlighted. Study flaws regarding patient selection were mainly related to description and appropriateness of the randomization procedure and concealment of allocation, with only 9 and 5 of the studies meeting these criteria, respectively. Items related to blinding were not achieved by the majority of the studies. Only 3 of the studies used a double-blinded design.

Testing subjects' adherence to intervention or having adequate adherence was another issue that was not accomplished by many studies (only 8 and 6 studies respectively). Furthermore, adverse effects were only reported by 3 of the studies and none of the studies provided details of the follow up period.

Despite the fact that the adequate handling of dropouts is considered an important method used to prevent bias in data analysis, only 11 of the analyzed studies included information regarding the rate of withdrawals/dropouts. The outcome measures were not described well in terms of validity, reliability, or responsiveness.

Regarding statistical issues, it was uncertain if sample size was adequate in 15 of the studies. Intention to treat analysis was used only in 11 of the studies. Finally, it also was unclear whether extraneous factors such as equipment calibration or medications during the duration of the study could affect the treatment responsiveness for IFC. For example, only 2 studies (10%) reported that the IFC equipment was calibrated at the time or during the study procedure.

Table 2.
Methodological Quality of the Studies[a]

Study	Item Scoring																																			Score/ Rating
	Patient Selection						Blinding				Interventions													Outcomes					Statistics							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	
Adedoyin et al,[47] 2002	0	0	1	0	0	1	0	0	1	1	0	0	1	1	1	0	0	0	0	n/a	n/a	n/a	0	n/a	n/a	n/a	1	1	1	0	0	1	1	1	1	0	0	1	1	0.48 Moderate
Adedoyin et al,[48] 2005	1	1	1	0	0	1	0	0	0	1	0	0	1	n/a	0	0	0	0	0	0	0	0	0	n/a	n/a	n/a	1	1	1	0	0	0	1	1	1	0	0	1	0	0.37 Poor
Adedoyin et al,[49] 2005	1	1	1	0	0	1	0	0	1	1	0	0	1	0	1	1	1	0	0	1	1	1	0	n/a	n/a	n/a	1	1	1	1	0	0	1	0	1	1	1	1	0	0.61 Moderate
Almeida et al,[50] 2003	1	1	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0	0	1	0	0	0	n/a	n/a	n/a	1	1	1	0	0	0	1	1	1	0	0	1	0	0.44 Moderate
Atamaz et al,[51] 2006	1	1	1	0	0	1	0	0	0	0	0	0	0	n/a	1	0	0	0	0	1	1	1	0	0	1	1	1	1	1	0	0	0	1	1	1	0	0	1	0	0.45 Moderate
Burch et al,[52] 2008	1	1	1	1	1	1	0	1	1	1	0	0	1	0	0	0	0	1	0	1	1	1	1	n/a	n/a	n/a	1	1	1	1	0	0	1	1	1	1	0	1	0	0.72 High
Cheing et al,[53] 2008	1	1	1	0	0	1	1	0	1	0	0	0	1	1	0	0	0	1	0	1	1	1	0	0	1	1	1	1	1	1	0	0	1	1	1	0	0	1	1	0.61 Moderate
Defrin et al,[54] 2005	1	1	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	n/a	n/a	n/a	1	1	1	0	0	0	1	1	1	0	0	1	0	0.42 Moderate
Hou et al,[55] 2002	1	1	1	0	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1	n/a	n/a	n/a	0	n/a	n/a	n/a	1	0	1	0	0	0	1	1	1	1	0	1	1	0.51 Moderate
Hurley et al,[56] 2004	1	1	1	1	1	1	0	0	0	0	0	0	1	0	1	0	1	1	1	1	0	1	1	0	1	1	1	0	1	1	0	1	1	1	1	1	0	1	1	0.66 Moderate
Hurley et al,[57] 2001	1	1	1	1	1	1	0	0	0	0	1	0	1	1	0	0	0	0	0	1	1	1	0	0	1	1	1	1	1	1	0	1	1	0	1	1	0	1	1	0.61 Moderate
Jarit et al,[58] 2003	1	1	1	0	0	1	0	1	1	1	1	0	1	1	1	0	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	1	0	1	1	0	0	1	0	0.54 Moderate
Lau et al,[66] 2008	1	1	1	1	1	0	0	1	1	0	0	0	1	0	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	0.72 High
Quirk et al,[59] 1985	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	1	1	1	0	0	0	1	1	1	0	0	0	0	0	1	0	0	0	0	1	0	0.36 Poor
Taskaynatan et al,[60] 2007	1	1	1	0	0	1	0	0	1	0	0	0	0	0	n/a	1	1	1	0	0	n/a	n/a	1	0	0	1	1	1	1	0	0	0	1	1	1	0	0	1	1	0.51 Moderate
Taylor et al,[61] 1987	1	1	1	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	n/a	n/a	0	n/a	n/a	n/a	1	1	1	0	0	0	1	1	1	0	0	1	0	0.39 Poor
van der Heijden et al,[62] 1999	1	1	1	1	0	1	0	1	1	1	0	0	1	n/a	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	0.78 High
Werners et al,[63] 1999	1	1	1	1	1	1	0	0	0	0	0	0	1	n/a	0	0	0	1	1	1	1	0	0	0	0	1	1	0	1	0	0	0	1	1	1	1	1	1	1	0.56 Moderate
Zambito et al,[64] 2007	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	0	0	n/a	n/a	n/a	0	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	0.67 Moderate
Zambito et al,[65] 2006	1	1	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	0	0	n/a	n/a	n/a	0	0	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	0.67 Moderate
Accomplished items	19	19	20	9	5	13	3	7	11	9	2	0	17	9	13	7	11	8	6	11	9	8	3	0	10	12	20	14	19	6	1	5	20	16	19	10	5	20	11	
Total percentage	95	95	100	45	25	68	15	35	55	45	10	0	85	60	65	35	55	40	30	79	64	57	15	0	83	100	100	70	95	30	5	25	100	80	95	50	25	100	55	

[a] 1=eligibility criteria; 2=described as randomized; 3=randomization performed; 4=randomization described as appropriate; 5=randomization concealed; 6=baseline comparability; 7=described as double blind; 8=blinding described an appropriate; 9=blinding of investigator/assessor; 10=blinding of subject/patient; 11=blinding of therapist; 12=blinding of the outcome (results); 13=treatment protocol adequately described for the treatment and control groups; 14=control and placebo adequate; 15=cointerventions avoided or comparable; 16=cointerventions reported for each group separately; 17=control for cointerventions in design; 18=testing of subject adherence; 19=adherence acceptable in all groups; 20=description of withdrawals and dropouts; 21=withdrawals/dropouts rate described and acceptable; 22=reasons for dropouts; 23=adverse effects described; 24=follow-up details reported; 25=follow-up period adequate; 26=short follow-up performed; 27=timing of outcomes comparable in all groups; 28=description of outcome measures; 29=relevant outcomes included; 30=validity reported for main outcome measure; 31=responsiveness reported for main outcome measure; 32=reliability reported for main outcome measure; 33=use of quantitative outcome measures; 34=descriptive measures reported for the main outcome; 35=appropriate statistical analysis included; 36=sample size calculated *a priori*; 37=adequate sample size; 38=sample size described for each group; 39=intention-to-treat analysis included; n/a=not applicable.

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3.3.3. IFC AND TYPE OF PAIN MANAGEMENT

The effect of IFC has been predominantly studied in patients with chronic painful conditions (16 of 20 trials examined).These included knee osteoarthritis, [47, 49, 51, 52, 54, 59] chronic low back pain, [48, 63-65] soft tissue shoulder pain,[53, 60, 62] fibromyalgia [50], chronic jaw pain [61], myofascial syndrome pain [55]. In contrast, the analysis of IFC in acute pain included just 4 articles; 3 of them related to acute low back pain and 1 in postoperative knee pain.

3.3.4. META-ANALYSIS RESULTS

Fourteen studies were included in the meta-analysis (Fig. 1) [47, 49-56, 60, 61, 63-66] with an overall sample size of 1,114 patients. Six studies were excluded for the following reasons: information regarding data variability (i.e. mean and SD) was not present,[58, 59] the unit of variability included was different than the standard deviation (i.e. interquartile range, median),[57, 62] the comparison included in the trial was not relevant for the study's purpose,[48] and the interventions included in the trial were too heterogeneous [51] (i.e. IFC, Infrared, shortwave diathermy, and 2 drugs (Sodium Hyaluronate and hylan G-F 20).

The 14 selected studies were chosen since they provided complete information on the outcomes evaluated and homogeneity regarding outcome measures. Of these studies, 4[54, 56, 61, 63] addressed the analgesic effect of IFC alone and 10 [47, 49, 50, 52, 53, 55, 60, 64-66] evaluated the effect of IFC applied as adjunct in a multimodal treatment

protocol. In addition, of these 14 studies, 3 [53, 54, 66] compared the effectiveness of IFC with a control group, 6 [47, 50, 54, 61, 64, 65] investigated IFC against placebo, and 7 [49, 51-53, 55, 56, 60, 63] compared IFC with another intervention such as manual therapy or exercise.

3.3.5. COMPARISON 1: IFC ALONE VERSUS PLACEBO GROUP ON PAIN INTENSITY AT DISCHARGE

Two studies [54, 61] were included in this comparison. One study [54] measured outcomes at discharge after 4 weeks of therapy and the other study measured outcomes after 1 week of therapy.[61] One trial[54] studied the effect of IFC on knee osteoarthritis, and the other trial studied the effect of IFC on temporomandibular joint pain.[61] One study was rated of moderate methodological quality[54] and the other study was rated of poor quality.[61] In this comparison both studies had opposite results regarding the effectiveness of IFC when compared with placebo group (Fig. 2). The pooled mean difference (MD) obtained for this analysis was 1.17 (95% CI =1.70 to 4.05). These results indicate that IFC alone was not significantly better than placebo at discharge.

Study or Subgroup	IFC Alone			Placebo			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Defrin et al,[54] 2005	2.1	0.5	12	−0.5	0.7	9	51.4%	2.60 (2.06, 3.14)	
Taylor et al,[61] 1987	1.75	1.96	20	2.08	1.53	20	48.6%	−0.33 (−1.42, 0.76)	
Total (95% CI)			32			29	100.0%	1.17 (−1.70, 4.05)	
Heterogeneity: tau^2=4.10, χ^2=22.33, *df*=1 (*P*<.00001), I^2=96%									
Test for overall effect: *z*=0.80 (*P*=.42)									

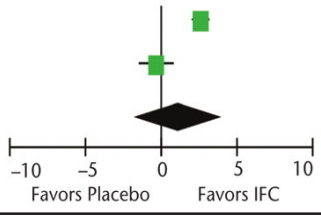

Figure 2. Forest plot comparison: interferential current therapy (IFC) alone versus placebo treatment on pain intensity at 1 week and 4 weeks (data presented as change scores). IV=inverse variance, 95% CI=95% confidence interval.

3.3.6. COMPARISON 2: IFC ALONE VERSUS COMPARISON GROUP ON PAIN INTENSITY AT DISCHARGE

Two studies,[56, 63] were included in this comparison. One study[63] measured outcomes at discharge after 2-3-weeks of treatment and the study measured outcomes after 8 weeks.[56] One trial studied the effect of IFC on acute low back pain, [56]and the other trial studied the effect of IFC on chronic

low back pain[63]. Both studies were of moderate methodological quality. In this comparison, both studies agreed that IFC was not significantly better than manual therapy or traction and massage (Fig. 3). The pooled MD obtained for this analysis was -0.16 (95% CI =0.62 to 0.31). These results indicate that IFC alone was not significantly better than any of the comparisons at discharge from therapy.

Study or Subgroup	IFC Alone Mean	IFC Alone SD	IFC Alone Total	Comparison Mean	Comparison SD	Comparison Total	Weight	Mean Difference IV, Random 95% CI
Hurley et al,[56] 2004	2.13	2.49	65	1.99	2.5	63	29.1%	0.14 (−0.72, 1.00)
Werners et al,[63] 1999	0.42	1.35	50	0.7	1.49	51	70.9%	−0.28 (−0.83, 0.27)
Total (95% CI)			115			114	100.0%	−0.16 (−0.62, 0.31)
Heterogeneity: tau²=0.00, χ^2=0.64, *df*=1 (*P*=.42), I^2=0%								
Test for overall effect: *z*=0.66 (*P*=.51)								

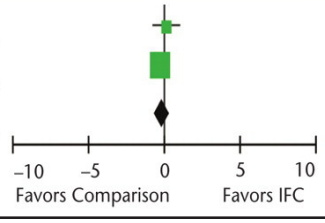

Figure 3. Forest plot comparison: interferential current therapy (IFC) alone versus comparison treatment on pain intensity at 3 week and 8 weeks (data presented as change scores). IV=inverse variance, 95% CI=95% confidence interval.

3.3.7. COMPARISON 3: IFC AS A SUPPLEMENT TO ANOTHER TREATMENT VS. CONTROL GROUP ON PAIN INTENSITY AT DISCHARGE

Three studies [53, 54, 66] were included in this comparison. Two studies used a 4-week discharge period,[53, 54] and one study used a one day discharge period.[66] One trial [54] studied the effect of IFC on knee osteoarthritis, another trial studied the effect of IFC [53] on frozen shoulder, and the third trial studied the effect of IFC on acute LBP.[66] Two studies included in this comparison were of moderate methodological quality[53, 54] and one study was considered to be of high quality.[66] In this comparison, the three studies tended to significantly favor the IFC applied as a co-intervention when compared with the control group (Fig. 4). The pooled MD obtained for this analysis was 2.45 (95% CI = 1.69 to 3.22). Thus, IFC applied as a co-intervention was over 2 points better on VAS in reducing pain intensity when compared with a control group in these conditions.

Study or Subgroup	IFC Therapy as Supplement Mean	SD	Total	Control Group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cheing et al,[53] 2008	3.02	1.94	23	0.08	2.13	24	23.0%	2.94 (1.78, 4.10)
Defrin et al,[54] 2005	2.1	0.5	12	−0.7	0.7	8	38.9%	2.80 (2.24, 3.36)
Lau et al,[66] 2008	2.2	1.65	55	0.4	1.5	55	38.1%	1.80 (1.21, 2.39)
Total (95% CI)			90			87	100.0%	2.45 (1.69, 3.22)
Heterogeneity: tau^2=0.31; χ^2=6.76, *df*=2 (*P*=.03), I^2=70%								
Test for overall effect: z=6.28 (*P*<.00001)								

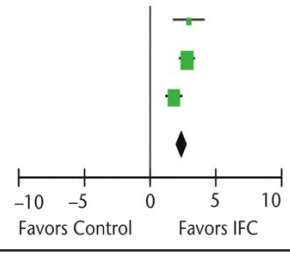

Figure 4. Forest plot comparison: interferential current therapy (IFC) as a supplemental treatment versus control treatment on pain intensity at 1 day and 4 weeks (data presented as change scores). IV=inverse variance, 95% CI=95% confidence interval.

3.3.8. COMPARISON 4: IFC AS A SUPPLEMENT TO ANOTHER TREATMENT VS. PLACEBO ON PAIN INTENSITY AT DISCHARGE

Five studies [47, 50, 54, 64, 65] were included in this comparison. Different times of discharge were used in the studies ranging from 2 weeks [64, 65] to 4 weeks.[47, 50, 54] Mean difference to pool the data was used. In addition, 95% CI and the random effect model were chosen. In this comparison, 3 studies [47, 50, 54] of moderate quality tended to significantly favor the IFC as a co-intervention when compared with placebo. One study, [64] of moderate methodological quality tended to significantly favor the placebo group. One study, of moderate quality, did not favor either IFC as a co-intervention or placebo (Fig. 5 upper part).[61, 65] The pooled MD obtained for this analysis was 1.60 (95% CI = -0.13 to 3.34). This finding indicates that although IFC as a co-intervention was statistically significantly better than placebo at decreasing pain intensity at discharge in conditions such as osteoarthritis, chronic low back pain, or fibromyalgia, IFC

tended to reduce pain in these conditions when compared with a placebo condition In addition,, the heterogeneity among studies was $I^{2=}96\%$ which is considered substantial according to Cochrane group guidelines [45]. Therefore, these results should be interpreted with caution. In this comparison, two studies [64, 65] provided follow-up data (3 months). Thus, an analysis at three months follow-up was performed (Fig. 5 lower part). The pooled MD obtained for this analysis was 1.85 (95% CI= 1.47 to 2.23). The two studies significantly favored IFC when compared with the placebo. This indicates that IFC as a co-intervention was better than placebo at decreasing pain intensity at 3 month follow up.

Study or Subgroup	IFC Therapy as Supplement Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 Pain at discharge (1 week, 2 weeks, 4 weeks)								
Zambito et al,[64] 2007	1.9	0.78	35	2.6	1	35	21.5%	−0.70 (−1.12, −0.28)
Zambito et al,[65] 2006	1.8	1.27	45	1.7	1.65	30	21.0%	0.10 (−0.60, 0.80)
Adedoyin et al,[47] 2002	6.87	1.2	15	4.5	2.79	15	18.6%	2.37 (0.83, 3.91)
Defrin et al,[54] 2005	2.1	0.5	12	−0.5	0.7	9	21.3%	2.60 (2.06, 3.14)
Almeida et al,[50] 2003	4.2	2	9	0	1.82	8	17.6%	4.20 (2.38, 6.02)
Subtotal (95% CI)			116			97	100.0%	1.60 (−0.13, 3.34)
Heterogeneity: $tau^2=3.59$, $\chi^2=112.03$, $df=4$ ($P<.00001$), $I^2=96\%$								
Test for overall effect: $z=1.81$ ($P=.07$)								
3.1.2 Pain up to 3-month follow-up								
Zambito et al,[64] 2007	3.8	1.1	35	2	0.71	35	76.1%	1.80 (1.37, 2.23)
Zambito et al,[65] 2006	3.2	1.64	45	1.2	1.7	30	23.9%	2.00 (1.23, 2.77)
Subtotal (95% CI)			80			65	100.0%	1.85 (1.47, 2.23)
Heterogeneity: $tau^2=0.00$, $\chi^2=0.02$, $df=1$ ($P=.66$), $I^2=0\%$								
Test for overall effect: $z=9.57$ ($P<.00001$)								

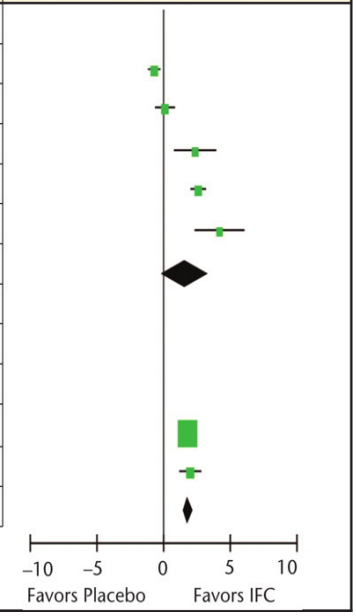

Figure 5. Forest plot comparison: interferential current therapy (IFC) as a supplemental treatment versus placebo treatment on pain intensity at 1-week, 2-week, 4-week, and 3-month follow-ups (data presented as change scores). IV=inverse variance, 95% CI=95% confidence interval.

3.3.9. COMPARISON 5: IFC AS A SUPPLEMENT TO ANOTHER TREATMENT VS. COMPARISON ON PAIN INTENSITY AT DISCHARGE

Five studies [49, 52, 53, 55, 60] were included in this comparison (Fig. 6). Different times of discharge were used ranging from 1 day [55] to 4 weeks[49, 53, 60] to 2 months. Two studies [49, 52] evaluated the effectiveness of IFC as a co-intervention for knee osteoarthritis, 2 studies evaluated the effectiveness of IFC as a co-intervention for shoulder pain,[53, 60] and one study evaluated the effectiveness of IFC as a co-intervention for myofascial pain. [55]

One study [55] compared IFC plus hot packs, active range of motion, and myofascial release with 5 different treatment modalities; thus, different analyses were run in order to determine the effect of IFC as a co-intervention when compared to all of these modalities (sensitivity analysis). We used the MD to pool the data. In addition, 95% CI and the random effect model were chosen.

In this comparison, no clear trend favoring either IFC as a co-intervention or the comparison treatments was observed for any of the analyses performed (Fig. 6). The pooled MD obtained for the various analyses was 0.55 (95% CI= -0.33. to 1.44). The mean difference indicated that IFC as a co-intervention was no better than other conventional treatments such as exercise, transcutaneous electrical nerve stimulation or ultrasound plus hot packs at decreasing pain intensity at discharge.

Study or Subgroup	IFC as Supplement			Comparison			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Adedoyin et al,[49] 2005	5.07	1.39	16	4.74	1.14	15	20.1%	0.33 (−0.56, 1.22)	
Burch et al,[52] 2008	2.79	1.32	53	2.32	1.54	53	23.1%	0.47 (−0.08, 1.02)	
Cheing et al,[53] 2008	3.17	1.94	23	3.04	1.97	24	18.0%	0.13 (−0.99, 1.25)	
Hou et al,[55] 2002 (B1)	3.34	1.14	9	0.77	1.8	21	18.5%	2.57 (1.50, 3.64)	
Taskaynatan et al,[60] 2007	0.8	1.49	21	1.4	1.59	26	20.2%	−0.60 (−1.48, 0.28)	
Total (95% CI)			122			139	100.0%	0.55 (−0.33, 1.44)	
Heterogeneity: $tau^2=0.80$, $\chi^2=20.86$, $df=4$ ($P=.0003$), $I^2=81\%$									
Test for overall effect: $z=1.22$ ($P=.22$)									

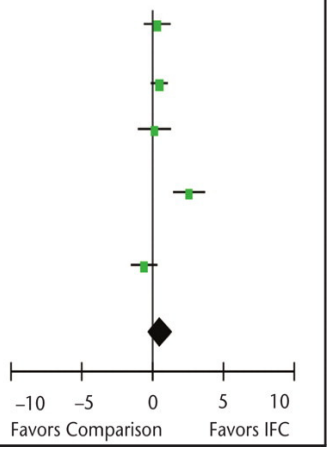

Figure 6. Forest plot comparison: interferential current therapy (IFC) as a supplemental treatment versus comparison treatment on pain intensity at 1day, 2 weeks, 4 weeks, and 2 months (data presented as change scores). IV=inverse variance, 95% CI=95% confidence interval. B1= hot pack + active range of motion.

3.4. DISCUSSION

3.4.1. ANALYSIS OF THE ANALGESIC EFFECT OF IFC ALONE

The results of this meta-analysis indicate that IFC applied alone as a treatment for musculoskeletal pain is not significantly better than placebo or comparison therapy (ie, manual therapy, traction, massage) at discharge from physical therapy. However, few included studies (27%) looked at the clinical analgesic effectiveness of IFC as a single therapeutic modality and most did not focus on a specific musculoskeletal disorder. We also observed differences in length of treatment (i.e. 1, 2, 3, and 8 weeks) as well as type of pain (i.e. acute or chronic),

indicating no consensus on optimal treatment parameters, which potentially contributed to the non-significance of the results.

3.4.2. ANALYSIS OF THE ANALGESIC EFFECT OF IFC AS PART OF A MULTIMODAL PROTOCOL (COINTERVENTIONS)

An important factor in this meta-analysis was the inclusion and analysis of studies including the application of IFC as a co-intervention in a multimodal treatment protocol. This decision was clinically sound because IFC is mainly used as an adjunct treatment. The results of this study indicate that IFC as a cointervention is significantly better than control and placebo for reducing chronic musculoskeletal pain at discharge and at 3 months posttreatment respectively. The pooled effect for IFC as a cointervention versus control was 2.45 in VAS [95% CI= 1.69 to 3.22]. According to some authors, this change is considered a clinically meaningful effect for acute painful conditions.[116-119] However, in chronic pain, a more stringent criterion seems to operate because a relative pain reduction of 50% or at least 3 cm on a VAS has been recommended for detecting a clinically successful pain reduction.[120, 121]

In addition, when IFC as a cointervention was compared with placebo at discharge, there was no statistically significant difference between the groups. At 3-month follow up, IFC as a co-intervention obtained a better effect on the VAS, although less pronounced than when compared with a control group (pooled effect = 1.85, 95% CI= 1.47 to 2.23). Thus, it seems that although IFC applied as a co-

intervention may have a modest analgesic effect, the magnitude of the effect is not large enough to be considered clinically relevant when compared with placebo or comparison interventions.

Because this is the first meta-analysis looking at the analgesic effects of IFC, direct comparisons cannot be made. In a previous study, Johnson and Martinson[122] concluded that transcutaneous electrical nerve stimulation, used mainly as an isolated intervention, provided significant pain relief when compared to placebo in a variety of chronic musculoskeletal conditions. Although methodological differences are present between both meta-analyses, some similarities such as the final sample sizes included, the focus on chronic musculoskeletal conditions, and the clinical heterogeneity makes the comparison between these two meta-analyses worth considering.

Some factors regarding IFC treatment may have accounted for the modest effect size observed. For example, although the stimulation of small diameter fibers have been demonstrated to produce a more positive effect for chronic pain when compared to the stimulation of large diameter fibers (Aβ), [54] the included studies, regardless of the type of pain, used stimulation parameters that were mainly related to the stimulation of Aβ fibers and the pain gate mechanism. [11, 47-50, 52, 53, 56-58, 61, 62] Although the stimulation of large diameter fibers is acknowledged to produce a fast onset of analgesia, an important shortcoming is its short lasting analgesic effect.[123-125] Thus, it is plausible that in chronic pain, which was the

dominant condition in this review, the effectiveness of IFC under these stimulation parameters may have been attenuated, resulting in a small effect in reported pain reduction. Further research needs to be conducted to evaluate the effect of noxious stimulation (e.g. small diameter fibers) on IFC effectiveness especially in chronic pain.

Additionally, IFC has not been applied using a consistent treatment protocol. For example, similar AMF settings (≥ 80 Hz) were considered for treating either acute [56, 57] or chronic conditions.[47, 50, 53, 55, 64, 65] Moreover, under the same condition (e.g. osteoarthritis), the authors inconsistently applied fixed AMF frequencies (i.e. 80 Hz) [49] or sweep AMF frequencies (i.e. 1-150 Hz, 30 -60 Hz, 0-100 Hz).[52, 54, 59] Although experimental evidence has challenged the role of AMF as the main analgesic component of IFC, [36, 37, 85, 126] inconsistency in the use of this parameter in clinical settings requires consideration. Based on the current evidence, recommendations for optimal dosage when using IFC are not clear. It seems, however, that clinical evidence supports the fact that AMF should not be the most important parameter for clinical decision-making. This fact has been corroborated by recent experimental evidence as well.[80] Instead, the use of a sensory level of intensity appears to be a consistent and effective factor for the majority of studies. Although some variations in the number of treatments and the treatment time exist, it seems that 10-20 minutes of application for 2 to 4 weeks with a total of 12 sessions is the most common treatment protocol for IFC.[47-51, 53, 54, 59, 60, 62, 64, 65]

In this systematic review, 16 out of 20 studies evaluated the role of IFC in chronic rather than acute pain. Based on this fact, it seems that IFC has been applied more in the management of chronic painful conditions. This creates the need for additional studies evaluating the analgesic effect of IFC in acute painful conditions. Interestingly, and apparently in contrast to current clinical practice in which IFC is mostly used for short term pain relief, this meta-analysis provided information regarding potential positive long term benefits from IFC.[64, 65]

3.4.3. ADVERSE EFFECTS

An important safety feature when applying electrotherapy modalities is the report of adverse effects. Although IFC is considered a safe modality, its application has been associated with local adverse effects such as blisters, burns, bruising and swelling.[127, 128] Interestingly, only 3 studies [52, 56, 60] included reports of adverse effects as a result of IFC treatment. Two studies[56, 60] reported no complications, while one study[52] reported the presence of muscle soreness in one subject. Reporting adverse effects must be included as a mandatory aspect not only for the safety of patients, but also for the professional integrity of therapists.

3.4.4. METHODOLOGICAL ELEMENTS AFFECTING OBSERVED EFFECT

Even though the quality of the trials appraised was generally moderate, there are some methodological biases common to these studies that could have an impact on results. Selection bias could have existed since only 9 trials reported

appropriate randomization and only 5 trials reported concealment of allocation. Another potentially important bias was the lack of blinding, especially of the patients (9 studies) and assessors (11 studies). The outcome for this meta-analysis was pain which is a subjective outcome and dependent on the subject's report. Trials without appropriate randomization, concealment of allocation, and blinding tend to report an inaccurate treatment effect compared to trials that include these features. [129 130 131]

Other potential biases that could potentially have affected observed effects were the lack of an appropriate sample size (only 5 of the trials reported adequate sample size) and the inappropriate handling of withdraws and drop outs (only 11 trials used intention to treat analysis). Reporting clinical significance of results has become a relevant issue to demonstrate effectiveness of an intervention. Clinical significance provides the clinician with adequate information regarding the clinical impact of an intervention because it can identify when a meaningful change is produced.[132] Despite this message, the report of clinically meaningful changes in the present study was largely neglected with only 3 studies including this component.[56, 57, 62]

The present study used a compilation of items from all of the scales used in the physical therapy literature. Although some of the scales used in physical therapy (i.e. PEDro, Jadad) have been validated in some way, our recent analysis of health scales used to evaluate methodological quality determined that none of these scales are adequate for use alone.[42] Therefore, it was decided that all of these

scales would be used to assess methodological quality and we used a compilation of items to provide a comprehensive and sensitive evaluation of the quality of individual trials. However, further research investigating methodological predictors for determining trial quality in physical therapy are needed.

3.4.5. SUMMARY OF EVIDENCE

As an isolated treatment, IFC was not significantly better than placebo or other interventions. Conversely, when included in a multimodal treatment plan. IFC displayed a pain relieving effect (VAS reduction of over 2 points) when compared to control condition.

3.4.6. STRENGTHS

This meta-analysis is the first systematic investigation regarding the pain reducing effectiveness of IFC on musculoskeletal pain. A comprehensive search was made for all the published research in this area over a wide range of years (1950-2010). In addition, authors were contacted in an attempt to have complete and relevant information about the selected studies**.** The 20 RCT articles included in this review covered a broad spectrum of acute and chronic musculoskeletal conditions. IFC was analyzed as isolated intervention as well as part of a multimodal treatment plan. In addition, the study provided multiple analyses, including the comparison between IFC and placebo, between IFC and control, and IFC contrasted to different types of interventions.

3.4.7. LIMITATIONS

Outcome level

A main limitation of this meta-analysis is the presence of clinical heterogeneity in the study population or intervention in most of the comparisons, casting some doubt on the validity of our meta-analyses results.

Study and review level

A potential limitation is the omission of non-English publications; however, English is considered the primary scientific language. It also, has been reported that language-restricted meta-analyses only minimally overestimate treatment effects (~2% on average) when compared with language-inclusive meta-analyses.[114] Therefore, language-restricted meta-analyses do not appear to lead to biased estimates of intervention effectiveness.[133, 134] Applicability of results about the isolated effect of IFC on musculoskeletal pain is also limited, as only four studies addressed this issue**.** Another important limitation is that this study included only pain as outcome measure. It would be important to know whether or not outcomes such as disability or function could have been modified by the application of IFC.

3.5. CONCLUSIONS

3.5.1. IMPLICATIONS FOR PRACTICE

IFC included in a multimodal treatment plan seems to produce a pain relieving effect in acute and chronic musculoskeletal painful conditions when compared with no treatment or placebo. IFC combined with other interventions was shown to be more effective than placebo application at 3-month follow-up in subjects with chronic low back pain. However, it is evident that under this scenario, the unique effect of IFC is confounded by the impact of other therapeutic interventions. Moreover, it is still unknown whether or not the analgesic effect of IFC is superior to these concomitant interventions.

When IFC is applied alone, its effect does not differ from placebo or other interventions (.e, manual therapy, traction or massage). However, both the small number of trials evaluating the isolated effect of IFC, heterogeneity across studies included studies along with methodological limitations identified in these studies prevent conclusive statements regarding its analgesic efficacy.

3.5.2. IMPLICATIONS FOR RESEARCH

Since only four studies were identified that evaluated the isolated effect of IFC with mixed results, further research is needed examining this issue ideally in homogeneous clinical samples. Further research is also needed to study the effect of IFC on acute painful conditions. Also of interest would be the study of the

effect of IFC in chronic conditions using a theoretical framework for the selection of parameters associated with suprasegmental analgesic mechanisms (i.e. noxious stimulus) instead of sensory stimulation.

3.6. ACKNOWLEDGEMENTS

Alberta Provincial CIHR Training Program in Bone and Joint Health, Izaak Walton Killam scholarship from the University of Alberta, Canadian Institutes of Health Research, Government of Chile (MECESUP Program), University Catholic of Maule- Chile, and Physiotherapy Foundation of Canada through an Ann Collins Whitmore Memorial Award.

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CHAPTER 4

A PRELIMINARY INVESTIGATION INTO THE EFFECTS OF ACTIVE INTERFERENTIAL CURRENT THERAPY AND PLACEBO ON PRESSURE PAIN SENSITIVITY: A RANDOM CROSSOVER PLACEBO CONTROLLED STUDY

Objective: (1) To determine the effect of active and placebo interferential current on muscle pain sensitivity using an experimental mechanically induced pain model. (2) To evaluate the predictive role of expectations, gender, baseline muscle pain sensitivity, and intervention order on placebo response.

Design: Randomized placebo controlled cross-over trial. Setting: University research laboratory. Participants: Forty healthy volunteers (20 females, 20 males). Interventions: Active interferential current, placebo (sham) interferential current, and no treatment/control were applied to the lumbar area on different days. Main outcomes measures: Pressure pain thresholds and placebo response.

Results: The two-way ANOVA with repeated measures analysis determined a significant interaction between condition and time (P=0.002). Pairwise comparisons found differences between active interferential and the control condition at 15 minutes into treatment (mean difference=0.890kg/cm2, 95% CI 0.023 to 1.757, P=0.043) and at 30minutes into treatment (mean difference= 0.910kg/cm2, 95% CI 0.078 to 1.742, P=0.028). The increase in pressure pain

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thresholds between the active interferential and the control condition (1.12kg/cm2) was clinically meaningful. Logistic regression analysis showed that the condition sequence order was the only variable that predicted placebo response (odds ratio 9.7; P=0.028). If a subject started the sequence receiving placebo treatment first, the odds of responding to placebo would be approximately 10 times higher (i.e. 90% probability of being a placebo responder) than that of starting with an active treatment.

Conclusions: Active interferential was more efficient than control condition in decreasing muscle pain sensitivity. Placebo interferential was not significantly different from control. Treatment sequence demonstrated a strong association with placebo response. These findings have implications for future research characterizing and identifying placebo responders in physiotherapy.

4.1. INTRODUCTION

Interferential therapy is the transcutaneous application of alternating medium-frequency amplitude modulated electrical current at low frequency (0 to 250 Hz). [1-3] Interferential therapy is widely used by clinicians to provide pain-relief for a variety of conditions and patient populations. [4-8]

The application of this modality has been shown to decrease pain in the short term in knee osteoarthritis [9-12] postoperative knee pain [13], and fibromyalgia. [14] In addition, clinically meaningful effects at 3 and 6 months follow-up have been reported in patients with frozen shoulder, [15] and low back pain. [16, 17] In contrast, no hypoalgesic effects have been demonstrated in shoulder pain. [18,19]

Pressure algometry is the most common modality used to apply a uniform rate of pressure for inducing mechanical pain. [20-23] Among the various exogenous experimental pain models (i.e. electrical, mechanical, chemical), the mechanically-induced pain model is believed to assess deep tissue (i.e. muscle) reflecting its sensitivity to pain. [24, 25]

Pressure pain sensitivity, evaluated using the pressure pain threshold, is the most commonly used method for quantitative analysis of local muscle pain and tenderness. The assessment of pressure pain thresholds has been extensively used in both clinical, [23, 26, 27] and experimental conditions [22, 28, 29] to assess muscle pain sensitivity and to evaluate the efficacy of therapeutic interventions and pain relieving modalities in patients as well as healthy subjects. In addition, treatment-

induced changes in pressure pain thresholds observed in laboratory settings are believed to correlate well with changes in the clinical status of pain, and as such, algometry and the measurement of the pressure pain thresholds is considered a useful experimental model. [21]

Placebo effect represents the contextual and psychosocial aspect of every treatment surrounding the patient. [30] Despite the growing interest in studying its effect, the placebo still remains a relatively unexplored area of study in physiotherapy. Results of a literature search including PEDro, MEDLINE, Scopus, and Embase (1966–2009), found only one study [31] investigating the direct measure of the placebo effect of interferential therapy by comparing placebo interferential therapy against no intervention. Authors reported that placebo interferential therapy was better at modulating experimental ischemic pain compared to control, [31] however a degree of caution is required when interpreting these results due to the small sample size included (n= 12) and other methodological issues.

Thus, additional research is clearly needed to assess the effect of placebo as a pain modulator in controlled conditions. It is unclear if the reaction to placebo interferential therapy obtained in experimental ischemic pain is comparable to other models of experimental pain. For example, of interest would be to determine the magnitude of placebo interferential therapy in a mechanically-induced pain model in healthy subjects.

Similarly, although evidence suggests that patient expectations have a significant impact on outcomes, [32, 33] information regarding the role of gender, treatment sequence order (i.e. receiving placebo or active interferential therapy first), expectations, and muscle pain sensitivity as determinants of placebo analgesia in physiotherapy interventions is still lacking.

Therefore, the primary objective of this study was to determine the magnitude of the placebo interferential therapy effect on muscle pain sensitivity in an experimentally-induced mechanical pain in healthy subjects. We also aimed to identify the potential predictors of placebo response in subjects responding the placebo interferential therapy. A secondary objective was to determine the hypoalgesic effect of active interferential therapy on muscle pain sensitivity

4.2. METHODS

4.2.1. RESEARCH DESIGN

This study was a randomized placebo controlled cross-over trial design.

4.2.2. SUBJECTS

A convenience sample of 40 healthy students and staff from the University of Alberta was recruited consisting of 20 females and 20 males. This sample size was chosen based on *a priori* sample size calculations using $\alpha = 0.05$, power of 80% and an effect size of 0.25 for a repeated measures analysis. [34]

Specific inclusion criteria consisted of healthy subjects between the ages of 18 and 50 years, taking no analgesic medication, and subjects without previous experience in electrotherapy. Exclusion criteria were any painful musculoskeletal condition or any contraindications to electrotherapy. All subjects acknowledged their understanding and willingness to participate by providing signed consent. Every subject was reimbursed CAD$40 for their participation in the study. Approval of this study was obtained from the University of Alberta Health Research Ethics Committee.

4.2.3. INTERVENTION DESCRIPTION

Both active and placebo interferential therapy treatments were delivered with a calibrated Intellect Legend Stim electrical stimulator (Chattanooga Group Inc., Hixson, TN USA). Parameters for the active interferential therapy treatment included a carrier frequency of 4000 Hz that was not modulated (AMF= 0Hz). Thirty minutes of stimulation was applied using four electrodes placed over the lumbar (L_1) and sacral (S_2) areas (see Fig. 1), with the right erector spinae muscle targeted as central area of stimulation (4 cm to the right of the spinous process of L_4 level). [22] The current intensity for the treatment was at a sensory level. [13, 22, 35-37]

4.2.4. PLACEBO APPLICATION AND CONTROL CONDITION

The placebo treatment included sham interferential therapy. Thirty minutes of sham application was delivered in the same fashion as per the active interferential therapy treatment, except that the lead wires of the equipment were disconnected from the jack of their output channels. Thus, the subjects received no current output. The jack of the output channels was covered during the procedure. During the application the investigator's instructions were as follows: "I am going to apply a therapeutic current called subthreshold electrical stimulation which you might or might not be able to perceive beneath the electrodes. It is still unknown if this new type of stimulation is better than the standard stimulation". Subjects

were facing the equipment screen which displayed visual and output signals. The control condition consisted of no application of interferential therapy or placebo treatment. To keep the investigator responsible for the pressure pain threshold measurements blinded, the electrodes were positioned in the same arrangement as used for the active and placebo interferential therapy applications for 30 minutes. However, subjects were told that no treatment was delivered.

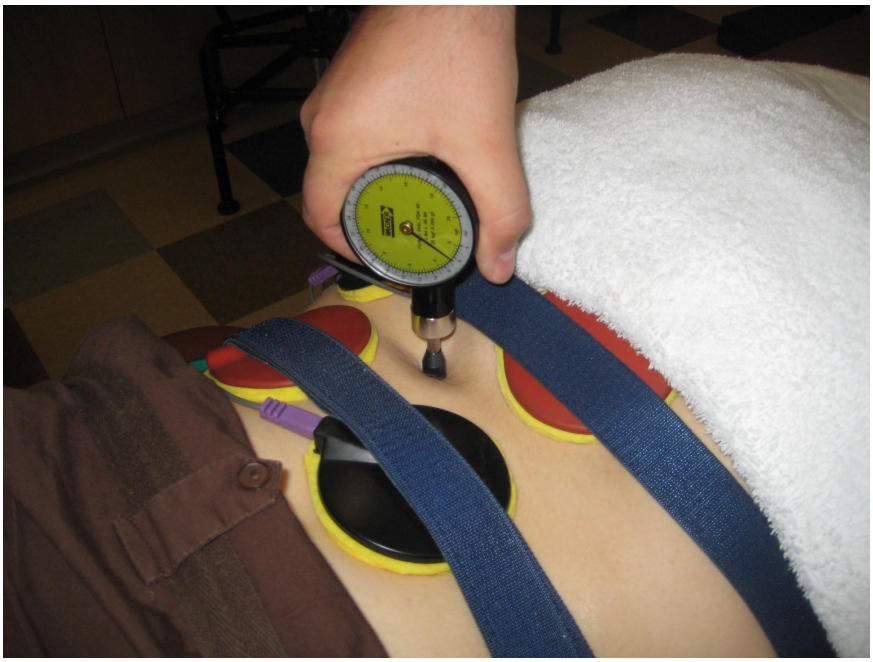

Fig. 1. Four carbon rubber electrodes placed over lumbar (L_1) and sacral (S_2) areas. Mechanical algometer applied perpendicularly over the right erector spinae muscle targeted as the central area of stimulation (4 cm to the right of the spinous process of L_4).

4.2.5. PLACEBO RESPONDER

A placebo responder was considered a subject with an increase in his/her pressure pain threshold of ≥ 1.1 kg/cm^2 as a result of the interferential therapy placebo intervention. This criterion was based on previous calculations of clinical significance for this outcome. [22, 38]

4.2.6. PRIMARY OUTCOME – PRESSURE PAIN THRESHOLD

Pressure pain sensitivity was evaluated through the pressure pain threshold, or the minimum pressure that induces pain or discomfort. [39] In this study, a mechanical algometer was used to determine the muscle pain sensitivity in the lumbar area. Pressure pain threshold measurements have been shown to have good or excellent inter-rater reliability (ICC 0.74 to 0.90) [40] and intra-rater reliability (ICC 0.75 to 0.99). [20, 23, 25, 41]

A trained physiotherapist assessor (JF) measured pressure pain thresholds by applying a calibrated mechanical algometer (Wagner Instruments, Greenwich, CT 06836-1217) at a constant rate of force of 1 kg/cm^2/second. The algometer was applied perpendicularly over the right erector spinae muscle, landmarked for reproducibility, 4 cm to the right of the spinous process of L_4 (see Fig. 1). The erector spinae muscle was chosen because it has previously been used in clinical, [42, 43] and experimental settings. [20, 22] Excellent intra-examiner reliability has been reported [20, 44] and normative values are available for this area. [44] The force

recorded by the algometer was the minimum amount of pressure that evoked the first sensation of pain. [21, 44]

4.2.7. GENERAL PROCEDURE

All subjects received both interferential therapy interventions (i.e. active and placebo) plus the control condition on separate days. The sequence order of treatment was randomized using a computerized table of random numbers. To avoid a carryover effect, treatments were applied with a washout period of at least one day of rest between. [22, 45, 46] A trained physiotherapist (SAO) applied the interferential therapy treatments. The subjects were blind to the interferential therapy interventions. The investigator (JF) in charge of measuring pressure pain thresholds was blind to the conditions and to the statistical analysis of data.

During the first visit, subjects were told that they would receive two interferential therapy treatments (i.e. active or placebo) based on different stimulation parameters or they could receive the control condition for 30 minutes according to the randomization order.

On the second and third visits, subjects received the other conditions as per the randomization procedure (Fig. 2). Before conducting the pressure pain threshold assessment, subjects were instructed in the application of the algometer and given a demonstration. They then underwent a practice test of pressure pain threshold

measurements using the dominant forearm until the subject felt they understood the sensation and what they were being asked to do and feel.

During the procedure of assessing pressure pain thresholds, patients were instructed to differentiate the pressure from a feeling of "being pressed" to "initial pain recognition (threshold)." [39] Subjects were asked to say "stop" as soon as they felt a clear sensation of pain, distinct from pressure or discomfort. The force recorded was the amount of pressure that evoked pain (pressure pain threshold).

Pressure pain threshold measurements were taken on four different occasions during the experimental procedure for each of the three conditions; M1 (10 min pre-treatment), M2 (time 0), M3 (15 min into treatment), M4 (30 min- end of treatment)) (see Fig. 3). On each occasion, two consecutive pressure pain threshold measurements performed 60 seconds apart were collected and averaged.

4.2.8. EXPECTANCY OF PAIN RELIEF MEASUREMENTS

Before and after the application of the three conditions, subjects were asked to rate their expectations of pain relief. The Credibility and Expectancy Questionnaire (CEQ) was used for this purpose. [47] The CEQ is considered to be a valid and reliable [47] tool to measure the expectancy construct.

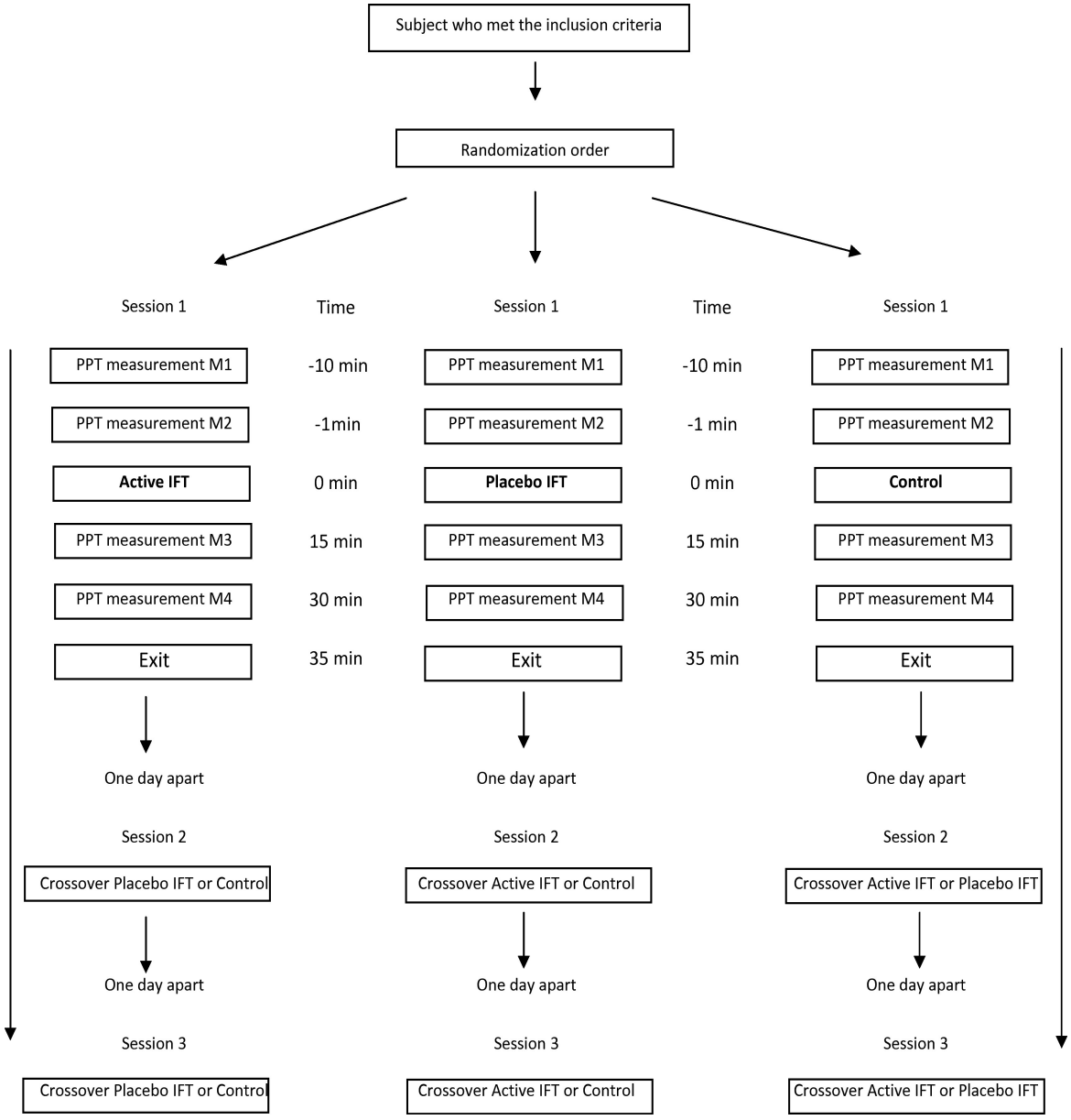

Fig. 2. Schematic sequence of the study procedure

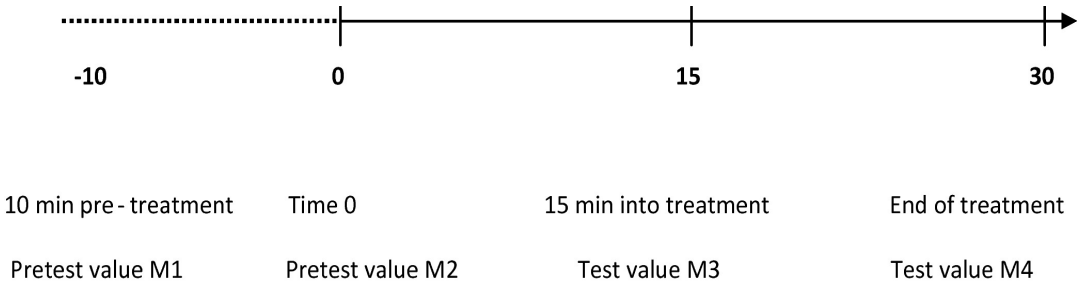

Fig. 3. The experimental procedure. Description of the recordings of Pressure Pain Thresholds at different time intervals during the study for the active, placebo and control conditions.

4.3. DATA ANALYSIS

A two-way ANOVA design with repeated measures was used to evaluate differences in pressure pain threshold values across measurement times among the conditions (i.e. active interferential therapy, placebo interferential therapy, and control). A Bonferroni's post hoc test was used to adjust for multiple comparisons during pairwise comparisons. The standard error of measurement value was calculated to determine clinical importance of the difference in the pressure pain threshold measurements. [48]

To identify the predictors of placebo analgesia, a multiple logistic regression analysis was performed. The outcome for this analysis was whether or not the subject was a placebo responder (yes/no= dichotomous variable) based on the previous established criterion ($\geq$ 1.1kg/cm^2). The predictors used in this model were gender (female/male), pre-treatment muscle pain sensitivity values

(continuous variable), levels of expectations for pain relief for the placebo interferential therapy (continuous variable) and interferential therapy order of treatment sequence (categorical variable with 3 categories: starting with placebo interferential current, starting with active interferential current, or starting with control) . The adjusted odds ratios were reported for each of the outcomes analyzed. The level of significance was set at $\alpha = 0.05$. Data analysis was performed blinded since each subject and condition was coded by an independent assistant not involved in the trial. The computer programs SPSS version 17.0 and STATA version 10 were used for all analyses (SPSS Inc. 233 S. Wacker Drive, Illinois USA, StataCorp LP 4905 Lakeway Drive College Station, Texas 77845 USA).

4.4. RESULTS

4.4.1. SUBJECTS

A total of 40 healthy volunteers, mean age 29.9 years (SD= 6.88, range = 19- 47 years), height 170.6 cm (SD= 8.26), weight 74.4 kg (SD= 14.49) were assessed for this study. No subjects were excluded. Regarding the treatment sequence, 15, 11 and 14 subjects received the active interferential therapy, the control condition, and the placebo interferential therapy as first intervention respectively.

4.4.2. MAIN EFFECTS OF INTERFERENTIAL THERAPY ON MUSCLE PAIN SENSITIVITY

No statistically significant differences among the three conditions (i.e. active interferential therapy , placebo interferential therapy , and control), regardless of time of evaluation for an increase in pressure pain threshold were found (mean difference between active interferential therapy and placebo interferential therapy = 0.079 kg/cm^2 , P = 1.0, [95% CI 0.700 to 0.857); mean difference between active interferential therapy and control = 0.461 kg/cm^2 , P = 0.385, [95% CI 0.281 to 1.203]; mean difference between placebo interferential therapy and control= - 0.382 kg/cm^2 , P = 0.254, [95% CI –0.922 to 0.158]).

4.4.3. INTERACTION BETWEEN TIME AND INTERFERENTIAL THERAPY APPLICATIONS ON MUSCLE PAIN SENSITIVITY

The two- way ANOVA determined that there was a significant interaction between condition and time of evaluation (P = 0.002). In addition, there was a significant main effect for time (P < 0.001) (Fig. 4). Pairwise comparisons found differences between the active interferential therapy and control conditions at 15 minutes (M3) (mean difference = 0.890 kg/cm2, P = 0.043, [CI 95% 0.023-1.757], and at 30 minutes (M4) (mean difference= 0.910, P = 0.028, [CI 0.078 – 1.742] (Table 1). No other differences were found between other conditions at different times.

4.4.4. PREDICTORS OF THE PLACEBO INTERFERENTIAL THERAPY RESPONSE

The results of the multiple logistic regression analysis showing the association (odds ratio) between gender, level of expectations before the intervention, muscle pain sensitivity, and order of sequence of treatment and placebo response are displayed in Table 2. The treatment sequence starting with active interferential therapy was used as a reference for the respective comparisons with either starting with control or placebo interferential therapy. The order of treatment sequence was the only variable that showed a significant association with placebo response after adjusting for gender, pre-treatment muscle pain sensitivity values, and expectancy levels. More specifically, when comparing subjects starting with placebo to subjects starting with active treatment, subjects starting the treatment sequence receiving placebo treatment first, had a 90% probability of being a placebo responder than a subject who started with an active treatment (reference comparison) [odds ratio=9.72; CI 95% CI (1.27 - 74.32); P =0.03]. No differences in placebo response were found between subjects starting with control interferential therapy condition when compared with starting with active interferential therapy.

No other variable included in the model, (i.e. pre-treatment muscle pain sensitivity values and expectancy levels) was significantly associated with the placebo response $P > 0.05$. Therefore, no interpretation can be reported.

4.4.5. BLINDING ASSESSMENT

The adequacy of blinding was assessed by calculating the difference in expectancy of pain relief scores (before and after) for the application of placebo and active interferential therapy. The mean difference in scores was -1.33 and –0.83 for the active and placebo interferential therapy treatments, respectively, with no significant differences between the treatments (P = 1.0). This provides some evidence that the blinding was adequate and that both treatments were valued similarly by the participants.

4.4.6. CLINICAL IMPORTANCE

The mean differences in pressure pain threshold between baseline and at 30 minutes of treatment for the active interferential therapy, placebo interferential therapy, and for the control application were 1.75 kg/cm^2, 1.02 kg/cm^2, and 0.620 kg/cm^2 respectively. The amount of change in pressure pain threshold calculated to be clinically important in this study was ≥ 1.16 kg/cm^2. Thus, the change in pressure pain threshold for the active interferential therapy achieved clinically meaningful levels.

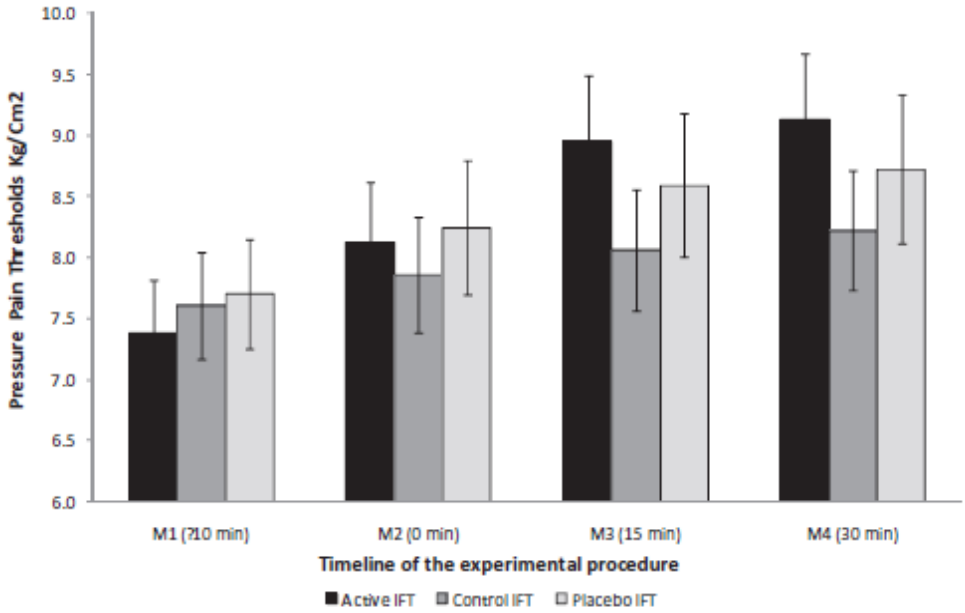

Fig. 4. Average Pressure Pain Thresholds ($Kg/cm^2/sec$) during the timeline of the experimental procedure for the three conditions (Active IFT, Placebo IFT and control). Results are shown as mean ± SEM

Table 1. Pairwise comparisons for interaction group x time.

Time	(I) group	(J) group	Mean difference (I – J)	95% confidence interval for difference[a]		Std. error	Sig.[a]
				Lower boundary	Upper boundary		
−10 minutes	1	2	−0.223	−1.111	0.666	0.355	1.000
		3	−0.325	−1.051	0.401	0.290	0.808
	2	1	0.223	−0.666	1.111	0.355	1.000
		3	−0.103	−0.698	0.493	0.238	1.000
	3	1	0.325	−0.401	1.051	0.290	0.808
		2	0.103	−0.493	0.698	0.238	1.000
0 minute	1	2	0.265	−0.514	1.044	0.312	1.000
		3	−0.125	−1.023	0.773	0.359	1.000
	2	1	−0.265	−1.044	0.514	0.312	1.000
		3	−0.390	−0.963	0.183	0.229	0.289
	3	1	0.125	−0.773	1.023	0.359	1.000
		2	0.390	−0.183	0.963	0.229	0.289
15 minutes	1	2	0.890*	0.023	1.757	0.347	0.043
		3	0.358	−0.522	1.237	0.351	0.946
	2	1	−0.890*	−1.757	−0.023	0.347	0.043
		3	−0.532	−1.276	0.211	0.297	0.243
	3	1	−0.358	−1.237	0.522	0.351	0.946
		2	0.532	−0.211	1.276	0.297	0.243
30 minutes	1	2	0.910*	0.078	1.742	0.333	0.028
		3	0.408	−0.557	1.372	0.385	0.890
	2	1	−0.91	−1.742	−0.078	0.333	0.028
		3	−0.502	−1.250	0.245	0.299	0.302
	3	1	−0.408	−1.372	0.557	0.385	0.890
		2	0.502	−0.245	1.250	0.299	0.302

Group 1 = active IFT, Group 2 = control, Group 3 = placebo IFT.
Based on estimated marginal means.
* The mean difference is significant at the 0.05 level.
[a] Adjustment for multiple comparisons: Bonferroni.

Table 2. Odds ratios measuring the association among gender, level of expectations before the intervention, muscle pain sensitivity, and order of sequence of treatment with placebo response considering the treatment sequence starting with active IFC as reference category

Placebo responder	Odds ratio	[95% CI]	Std. error	*P* value
Sex (dichotomous variable)				
Male	1.0			
Female	0.62	0.11 to 3.57	0.56	0.60
Expectancy level (continuous variable)	1.02	0.87 to 1.20	0.08	0.82
Muscle pain sensitivity (continuous variable)	1.37	0.93 to 2.02	0.27	0.11
Sequence order (categorical variable)				
Treatment starting with active IFC	1.0			
Treatment starting with control	2.46	0.406 to 14.86	2.26	0.33
Treatment starting with placebo	9.72	1.27 to 74.32	10.09	0.03

4.5. DISCUSSION

4.5.1. ANALGESIC EFFECTIVENESS OF INTERFERENTIAL THERAPY

In this study, active interferential therapy was shown to be more effective than a control condition in decreasing muscle pain sensitivity in healthy subjects. Our findings extend the conclusions of several clinical studies supporting the effectiveness of this modality for musculoskeletal pain [9-13, 15-17, 48-50] and experimental pain. [22, 28, 36, 45, 51-53] Also, although modest, the hypoalgesic effect of interferential therapy, as part of a multimodal plan in the management of musculoskeletal pain, has been recently documented. [54] Thus, since interferential therapy is able to produce a consistent hypoalgesic effect in both clinical and experimentally-induced pain, physiotherapists may have increased confidence in its clinical application.

A medium frequency of 4000 Hz with an amplitude modulated frequency (AMF) parameter of 0 Hz was included in this study. In a recent study we examined muscle pain sensitivities achieved when the AMF parameter was present (100 Hz) and absent (0 Hz). The two groups showed a comparable hypoalgesic effects indicating that the medium-frequency is likely to be the main stimulation parameter for interferential therapy. [22] The results of the present study tend to confirm this notion.

The minimal value considered for a clinically meaningful change in pressure pain threshold calculated for this study was 1.16 kg/cm^2. The mean difference in

pressure pain threshold between baseline and at 30 minutes of treatment for the active interferential therapy was clinically relevant (1.75 kg/cm^2). The magnitude of change between baseline and at 30 minutes of treatment for the active interferential therapy compared to the control condition was considered borderline (1.12 kg/cm^2). However, previous studies have reported that a change in pressure pain threshold of 1.10 kg/cm^2 represents a clinically important change. [22, 38] Based on these reports, the change in pressure pain threshold between baseline and at 30 minutes achieved by the placebo interferential therapy (1.02 kg/cm^2) could be considered approaching clinical significance.

Interestingly, the magnitude of change in pressure pain threshold for active interferential therapy in this study was appreciably higher (1.75 Kg/cm^2) compared with our previous study using a similar experimental pain model contrasting the effects of two active interferential therapy treatments in pressure pain threshold (0.76 Kg/cm^2). [22] Although direct comparison between the two studies cannot be made, this difference is important. We hypothesize that the reason for this difference in favor to the present study could have been the context and therapeutic encounter in which the treatments were applied. As opposed to the first study, in the present study we attempted to simulate a clinical context within the laboratory which included a treatment area. Thus, visual environmental cues such as models of the spine, posters regarding anatomy, and a elaborate adjustable table were displayed in the room. In addition, both researchers involved in the study wore formal clothes and white coats. This therapeutic context could also

explain why the placebo interferential therapy in this study was largely superior in decreasing muscle pain sensitivity (1.02 Kg/cm^2) compared with the active IFC treatment included in the previous study (0.76 Kg/cm^2).

4.5.2. PLACEBO EFFECTS OF INTERFERENTIAL THERAPY

In this study, placebo interferential was not more efficient than the control condition in decreasing muscle pain sensitivity. Some theories could be postulated to explain these results. First, the magnitude of the placebo effect is associated with the type of experimental pain model used. The mechanically-induced pain model is believed to assess deep tissue (i.e. muscle) reflecting its sensitivity to pain. [24, 25] However, the short-lasting acute stimulus associated may not parallel clinical pain. [55] Moreover, the placebo response in experimental pain increases when the stimulus is severe and long lasting. [56] In a recent meta-analysis regarding placebo mechanisms, the magnitude of placebo effect was reported to be larger (d= 0.96) in studies where pain was induced via long-duration stimuli (> 20 sec) when compared to studies where pain was induced via short-duration stimuli (d= 0.81). [57]

Based on these findings, we could interpret that the mechanical model of pain is likely not the most appropriate model to elicit a placebo response in healthy subjects.

Another plausible explanation could be the mechanisms involved to elicit the placebo response. The placebo effect in this study was induced only by verbal

suggestions. Evidence revealed that a combination of conditioning (association and learning) and suggestions showed a higher placebo response than suggestions alone or conditioning alone. [58] The verbal suggestions given to the subjects in this study were only moderate. Under this scenario, it is conceivable that the expectations for pain relief were not an important factor in eliciting a placebo response.

Finally, although some evidence supports a strong placebo analgesia in experimental pain [59] other evidence suggests a noticeable placebo effect in clinical pain. [60, 61] Studies exploring the variables contributing to the placebo response agree that high levels of anxiety, as observed in clinical research, tend to predict a placebo effect. [62-66]

Thus, while clinical pain subjects are prone to anxiety, uncertainty and apprehension, in a laboratory setting where a subject has volunteered and reassured about the safety of the procedure, using experimental pain likely arouses little if any anxiety. [56] We believe that the absence of the anxiety construct in laboratory conditions may have undermined the effect of placebo in our study. This hypothesis, although speculative, may explain in part the modest effect of placebo interferential therapy displayed in this study of healthy subjects undergoing a transient painful (i.e. mechanical) stimulus in experimentally controlled conditions.

In addition, it is believed that the placebo effect operates mainly on the affective component of pain. [67] Thus, in experimental conditions in which the pain is a

transient sensation with no emotional implications involved, expectations or desire for pain relief could be less pronounced than in clinical pain. However, further research is needed to investigate whether expectations are more relevant in subjects suffering from actual pain receiving physiotherapy and whether clinical pain is more sensitive than experimental pain to placebo analgesia.

4.5.3. DETERMINANTS OF PLACEBO INTERFERENTIAL THERAPY ANALGESIA

In this study differences in expectations, gender, and baseline muscle pain hypersensitivity did not account for differences in placebo effects. However, expectations for pain relief have been shown to mediate placebo analgesia in clinical [58, 63, 68] and experimental pain studies. [69-71] A probable reason for these dissonant results compared with previous experimental studies could be the different pain models used among the studies. For example, repeated electrical stimulation, as applied in these studies, could induce temporal summation, causing an increase in referred pain areas as well as an enhancement of perceived pain intensity. [72]. Thus, it appears reasonable that an electrical stimulus may be perceived by the subjects as a threat. Thus, the anxiety associated with the electrical experimental procedure could lead to greater need for pain relief and therefore a greater placebo response may be activated by this model of pain. [73]

Finally, it is believed that mechanisms underlying expectations are dynamic and its effects could be different depending on the type of pain involved (i.e. clinical

or experimental). [61] Although merely speculative, this notion could be extended between different types of experimental pain models involved when investigating the placebo response.

The only variable that predicted the placebo response was the sequence order of the intervention condition (i.e. starting with active interferential therapy or starting with placebo). If a subject started the sequence receiving placebo first, the odds of responding to placebo would be about 10 times higher than when starting with active treatment. Perhaps people not receiving a previous exposure to active interferential therapy might believe that the lack of stimulation associated with the placebo was indeed a truly active and effective intervention.

4.5.4. STRENGTHS AND LIMITATIONS OF THE STUDY

This is the first study exploring the effect of placebo interferential therapy on muscle pain sensitivity using a direct measure of its effects against a no intervention/treatment in a mechanically-induced pain model. In addition, the impact of several potential predictors of the placebo interferential therapy response was also investigated. The double blind, placebo controlled randomized design of this study facilitated rigorous control of potential confounders.

Some limitations have to be acknowledged. The results are only applicable to healthy subjects experiencing mechanically-induced pain. Hence, these results

cannot be generalized to clinical conditions. Finally, the level of verbal suggestion given to the subjects in this study was only moderate.

4.5.5. FUTURE DIRECTIONS

It is probable that placebo interferential therapy in clinical pain might have a different effect when compared to experimental pain. Research must be conducted to confirm this impression. Physiotherapy encompasses a high degree of therapist-patient interaction, expectancies and other contextual factors. These features should be further investigated to determine their contribution to the placebo effect of physiotherapy in clinical pain. Research should be conducted to assess the effect of stronger verbal suggestions (e.g. "the intervention you are going to receive is a highly effective pain reliever") and expectations for pain relief related to the placebo response in physiotherapy interventions. Finally, efforts need to be focused in investigating the placebo effect as mechanism of change in clinical trials, and the potential exploitation of the therapeutic clinical context to the patient's benefit.

4.6. CONCLUSIONS

The active interferential therapy was shown to be more effective than control in decreasing muscle pain sensitivity in healthy subjects. Placebo interferential therapy treatment was not significantly different from the control condition. The difference in pressure pain threshold between active interferential therapy and

control condition reached clinically meaningful levels (1.12 Kg/cm^2). With regards to the placebo determinants of interferential therapy, the treatment condition sequence order was the only variable to predict a placebo response. These findings have major implications for future research characterizing and identifying placebo responders in physiotherapy along with increasing the design and efficacy of clinical trials.

Acknowledgments: The authors wish to thank Ben Vandermeer statistician in the Alberta Research Centre for Health Evidence (ARCHE).

Ethical approval: University of Alberta Research Ethics Committee (Ref. Nº 7535)

Funding: Catholic University of Maule and Rehab Med Faculty, University of Alberta

Conflict of interest: None declared

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CHAPTER 5

ENHANCED THERAPEUTIC ALLIANCE MODULATES PAIN INTENSITY AND MUSCLE PAIN SENSITIVITY IN PATIENTS WITH CHRONIC LOW BACK PAIN: A RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL.

Background: Mechanisms through which physiotherapy interventions influence chronic musculoskeletal pain are complex and include both the specific ingredient of an intervention as well as contextual factors inherent to clinical encounters, including the provider, patient and setting. Although well documented in other areas, the impact of contextual factors in the treatment of low back pain (LBP), when applying physiotherapy interventions, is unknown.

Methods: 117 chronic LBP participants were randomly divided into 4 groups: active limited (AL) included the application of active interferential current (IFC) in a limited therapeutic encounter (i.e. limited patient-practitioner interaction), sham limited (SL) included sham IFC in a limited therapeutic encounter, active enhanced (AE) included active IFC in an enhanced therapeutic encounter (i.e. supportive patient-practitioner relationship, encouragement), and sham enhanced (SE) included sham IFC in an enhanced therapeutic encounter. Outcomes included pain intensity (PI-NRS) and muscle pain sensitivity (PPT). Analysis

included MANOVA and clinical significance through the effect size and global rating scale.

Results: Baseline demographics data were similar ($p>0.05$) across conditions. There were statistically significant differences between groups on PPTs and PI-NRS (baseline and after treatment) ($p< 0.05$). Mean differences in PI-NRS were 18.3 mm, 10.0 mm, 31.4 mm, and 22.2 mm, for the groups AL, SL, AE, and SE, respectively. Clinically important effect sizes were found. Mean differences in PPTs were 1.2 kg, 0.3 kg, 2.0 kg, and 1.7 kg for the group AL, SL, AE, and SE, respectively. Again, clinically important effect sizes were found.

Conclusion: Results highlight the important role of contextual (i.e. non-specific) factors in the treatment of patients with chronic LBP. Specially, enhanced therapeutic relationship was associated with meaningful improvement in clinical outcomes. Factors other than the specific ingredient of a treatment may have a large role in achieving positive clinical outcomes, and exploring them is central to physiotherapy practice.

5.1. INTRODUCTION

Non- specific low back pain (LBP) is described as pain, muscle tension, or stiffness localized below the costal margin of the back and above the inferior gluteal folds, with or without leg pain (sciatica). [1] When it persists for 12 weeks or more, the condition is defined as chronic low back pain. [2] This condition is a highly prevalent problem that represents a challenge for health care providers and society. [3, 4] Disability and work absence associated with chronic low back pain involves millions of dollars worldwide due to the impact of lost productivity, compensation payments, treatment costs, and resource utilization.[4, 5] Common non-pharmacological interventions used by physiotherapists to treat chronic LBP include acupuncture, massage, thermotherapy, exercise, mobilization, manipulation, laser therapy, and electroanalgesia (e.g. transcutaneous electrical nerve stimulation (TENS) or interferential therapy (IFC)).

Mechanisms through which physiotherapy interventions influence chronic musculoskeletal pain are likely complex. Variables associated with the clinician, patient and setting may influence clinical outcomes in addition to the specific physical interventions used to address functional limitations. These factors make up 'the context' and can be described as 'nonspecific' or 'contextual'.[6] Examples include the clinician's words, the clinical environment, patient-practitioner relationship, nature of the therapist's clothing or uniform, and the appearance and sight of the therapeutic equipment.[7-9] When contextual factors produce a positive effect on clinical outcomes, it is known as contextual, nonspecific, or placebo

effect. The placebo effect is thus the positive psychosocial and neurobiological effect the context has on the patient.[8, 9]

Although in clinical practice both effects (i.e. specific and nonspecific) may work together to benefit patients, the estimation of the placebo effect, or contextual factors that surround a therapy, has not traditionally been a primary focus of investigation. A reason is found in the prevailing biomedical model in which illnesses can be treated with interventions based on specific modes of action. Also, regulatory requirements of clinical researchers encourage study designs demonstrating specificity of the active ingredients of a treatment.[10, 11]

However, empirical evidence stemming from placebo research shows that subjective outcomes (e.g. pain) [12-14] and objectively measurable physiologic function changes have been observed in response to placebo interventions in different conditions including immune, [15] endocrine, [16] respiratory and cardiovascular systems, [17] Parkinson's disease, [18, 19] and depression. [20, 21] In addition, neuroimaging studies have revealed two important findings. First, that placebo-induced analgesia decreases neural activity in pain processing areas of the brain, and second, that placebo and endogenous opioid peptides share the same network. [22-24] Thus, these data confirm that placebo represents a real phenomenon capable of producing biological effects on the body and brain.

Physiotherapy demands a comprehensive analysis of all factors that potentially could influence its clinical efficacy [25] especially in chronic pain states. Therapeutic contextual factors associated with the therapist, patient and setting may influence clinical outcomes in addition to the specific interventions used to

address specific functional limitations. Among the diverse therapeutic contextual factors, the therapeutic alliance (TA) is fundamental to the therapeutic process and the placebo effect in clinical practice. The TA can be defined as the working rapport or positive social connection between the patient and the therapist. [26] More specifically, during rehabilitation, TA relies on "a complex interplay of technical skill, communicative competence, and the reflective capacity of the therapist to respond to the patient in the moment of therapy" [27] (p.873). Thus, TA encompasses both the relational and interactional aspects of a rehabilitation partnership [28] When achieved in an effective manner, TA becomes a source of motivation, encouragement, and reassurance as well as an opportunity for revision of expectations by both the therapist and the patient. Therefore, an effective TA can lead to a therapeutic change for the patient.

The TA has been found correlated with treatment adherence and positive outcomes in several disciplines including medicine, psychotherapy, and physical rehabilitation.[29-36] Also, the contribution of this construct to therapeutic outcomes, [11, 37, 38] as well as its predictive power [39] has been determined in psychotherapy interventions. It has been argued that in psychotherapy, the TA explains more variance in outcome than the specific effect of interventions.[38, 40] Thus, it appears that, in psychotherapy, the elements of therapeutic change may lie in the therapeutic interaction (i.e. non-specific factors) rather than the specific ingredients of the interventions.[38] Although an identifiable "practitioner effect" has been documented for low back pain and neck pain intervention trials [41] this phenomenon has not systematically been investigated in treatments aimed at

modifying musculoskeletal pain. In physical rehabilitation, a recent systematic review pointed out that, a consistent pattern has been observed of positive TA being correlated with improved pain, disability and treatment satisfaction.[36] However, an estimate of the magnitude of this association is still unknown.[36] In addition, experimental manipulation of this construct is still needed for physiotherapy interventions in patients with painful musculoskeletal conditions to confirm a causal effect.

It is likely that the treatment context, and specifically the TA, may play a relevant role in the management of chronic pain in rehabilitation; however this hypothesis has not been yet confirmed. Indeed, to date, no randomized controlled trial has adequately tested the contributor role of therapeutic alliance in clinical outcomes on chronic low back pain. We therefore carried out a randomized clinical trial to compare the effect of an enhanced TA versus a limited TA on pain intensity and muscle pain sensitivity in patients with chronic low back pain receiving an interferential therapy (IFC) treatment. We hypothesized that:

1. Active IFC, applied in an enhanced TA would statistically and to a clinically important extent reduce pain intensity scores and decrease muscle pain sensitivity in patients with chronic low back pain, when compared to active IFC applied in a limited TA.
2. Sham IFC, applied in an enhanced TA, would statistically and to a clinically important extent reduce pain intensity scores and decrease muscle pain sensitivity in patients with chronic low back pain, when compared to sham IFC applied in a limited TA.

3. Sham IFC, applied in an enhanced TA, would statistically and to a clinically important extent reduce pain intensity scores and decrease muscle pain sensitivity in patients with chronic low back pain, when compared to active IFC applied in a limited TA.

5.2. METHODS

5.2.1. STUDY DESIGN

This study was a randomized double-blind, placebo-controlled design with repeated measures. One hundred and seventeen participants were randomly divided into 4 groups: active limited (AL) (n=30) included the application of active IFC in a limited therapeutic encounter (i.e. limited patient-therapist interaction), sham limited (SL) (n=29) included the application of sham IFC in a limited therapeutic encounter (i.e. limited patient-therapist interaction), active enhanced (AE) (n=29) included the application of active IFC in an enhanced therapeutic encounter (i.e. enhanced patient-therapist interaction), and sham enhanced (SE) (n=29) included the application of sham IFC in an enhanced therapeutic encounter (i.e. enhanced patient-therapist interaction). See Figure 1.

5.2.1.1. Randomization

A randomization sequence stratified by gender was computer-generated (Web site Randomization.com; http://www.randomization.com). The randomization sequence was generated by a research assistant not involved in patient recruitment and evaluation. This assistant distributed the results of the generated sequence

into envelopes that were consecutively numbered, opaque, and sealed. Eligible participates were allocated to the treatment groups (AL, SL, AE, SE) by a physical therapist who opened the next available numbered envelope prior to each treatment session.

5.2.1.2 Participants and recruitment

The study was conducted in the sports physical therapy laboratory of the Faculty of Rehabilitation Medicine at the University of Alberta, Edmonton, Canada. Patients with LBP were recruited voluntarily from the local community by a widely circulated poster advertisement. Inclusion criteria for participation were non-specific LPB of at least 3 month duration resulting in a mild to moderate level of disability (Oswestry disability index $\leq 60\%$), pain intensity score between 3 and 8 points (PI-NRS), and age between 18 and 65 years. Participants were excluded if they had any contraindications related to the use of electrotherapy, neurological problems (central or peripheral), concomitant physiotherapy or chiropractic treatment, fibromyalgia or general systemic disease conditions, and previous experience with electrical pain relieving modalities.The principal investigator contacted interested individuals by telephone or e-mail to ensure that the candidate met the inclusion criteria, and they were also interviewed to confirm eligibility prior to the application of the therapy.

5.2.1.3 Informed consent

All subjects acknowledged their understanding and willingness to participate by providing signed consent, but the consent disclosure omitted certain descriptors and information about the methods to protect the study's scientific validity. For

example, neither the word placebo nor the word sham was mentioned during the conversation. Also, to avoid biasing their opinions of interactions with the treating therapist, participants were not told about the different levels of therapeutic alliance associated with the treatments. Participants were informed that the study was a clinical trial aimed to determine the difference in effectiveness between the standard electrotherapy treatment for low back pain (i.e. active IFC) and a new treatment based on a sub-threshold level of electrical stimulation (i.e. sham IFC). Every subject was reimbursed CAD$20 for participation in the study. The University of Alberta Health Research Ethics Committee approved the study.

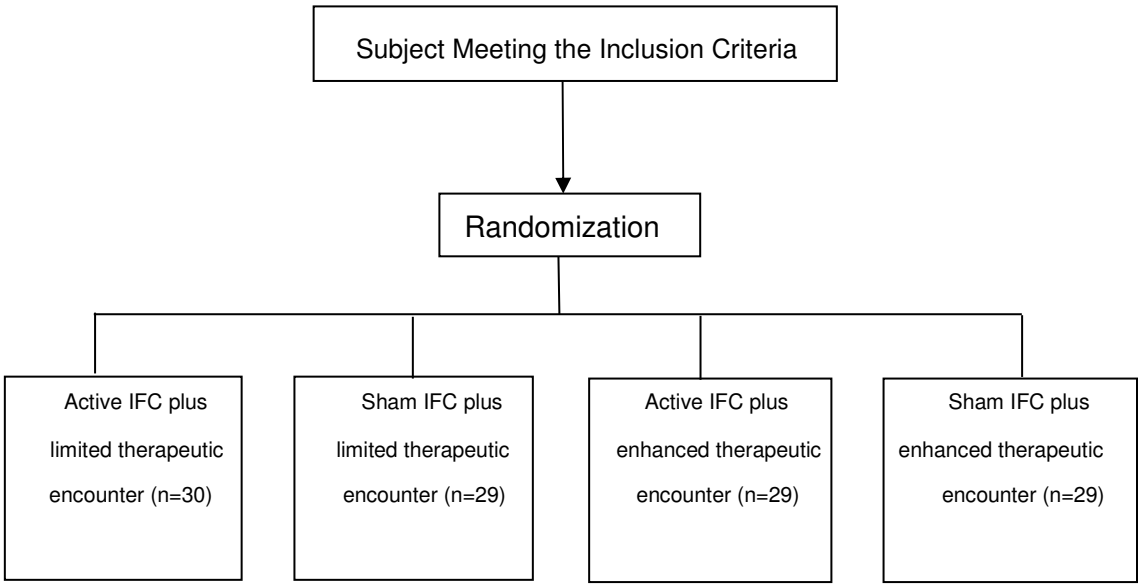

Figure 1. Schematic sequence of the study procedure

5.2.2. INTERVENTION COMPONENTS

Both the active limited and the active enhanced groups included application of an active IFC with four carbon rubber electrodes placed over the participants' lumbar area (see figure 2). The intensity of the current for treatment application was a strong but comfortable sensory level, producing a "pins and needles-like sensation" without visible muscle twitches.[45, 46] The frequency parameter was set at an AMF of 0 Hz. [45, 46] The participants assigned to the SL and SE groups received sham IFC treatment. This intervention was delivered using the same equipment and the same electrode arrangement as per the active IFC groups, except that the lead wires of the IFC equipment were disconnected from the jack of their output channels. Thus, the participants received no current output. The jack of the output channels was covered during the procedure and the equipment screen displayed the same visual and output signals as in the active treatment group. Thus, neither the participant nor the assessor was able to distinguish active or sham treatments.

These treatment protocols were adapted from a previous trial exploring the components of placebo effect in acupuncture treatment of irritable bowel syndrome. [47]

Group 1 *(Active IFC plus limited therapeutic interaction)*

For this group, a single 30-minute session of active IFC was applied with a limited patient-therapist interaction. The limited interaction included about 5

minutes during which the therapist introduced herself and explained the purpose of the treatment. In addition, participants were told that this was a "scientific study" for which the therapist was instructed not to converse with participants during treatment. [47]After setting up the treatment parameters, the therapist left the room but remained outside in case the patient required attention during the treatment. The therapist returned to the room only at 15 and 30 minutes into the treatment, to be present when the tester arrived to proceed with assessment of the muscle pain sensitivity outcome.

Group 2 *(Sham IFC plus limited therapeutic interaction)*

For this group, the same protocol as the one above described for the group 1 was applied. The difference was that for this group a sham IFC intervention was considered. During the sham application the investigator's instructions were as follows: "today I am going to apply a new treatment called therapeutic sub-threshold current…since the level of stimulation is sub-threshold, you might not be able to feel it beneath the electrodes".

Group 3 *(Active IFC plus enhanced therapeutic interaction)*

For this group, a single 30-minute session of active IFC was applied with an enhanced patient-therapist encounter. During the first ten minutes, participants were questioned about their symptoms, how LBP influenced her/his lifestyle, and how much the participant knew about the cause of her/his condition. The therapeutic interaction was enhanced through the inclusion of behaviors such as

active listening (i.e. repeating patient's words, asking for clarifications), empathy (such as saying: "I can understand how difficult LBP must be for you"), or twenty seconds of thoughtful silence while analyzing the treatment plan.[47] This intervention model aimed to create an optimal patient-clinician relationship.[47, 48] After completing this protocol, the therapist proceeded with the treatment application. The therapist stayed in the room during the entire treatment time. Also, during this time, verbal interaction between the therapist and participant was encouraged. In addition, the therapist remained in the treatment area when the tester arrived to proceed with the assessment of the muscle pain sensitivity outcome (i.e. 0 minutes, 15 and 30 minutes into the treatment). Finally, after finishing the treatment, a few words of encouragement were exchanged between the therapist and the participant.

Group 4 *(Sham IFC plus enhanced therapeutic encounter)*

For this group, the same protocol as the one above described for the group 3 was applied. The difference was that for this group a sham IFC intervention was considered. During the sham application the investigator's instructions were as follows: "today I am going to apply a new treatment called therapeutic sub-threshold current…since the level of stimulation is sub-threshold, you might not be able to feel it beneath the electrodes."

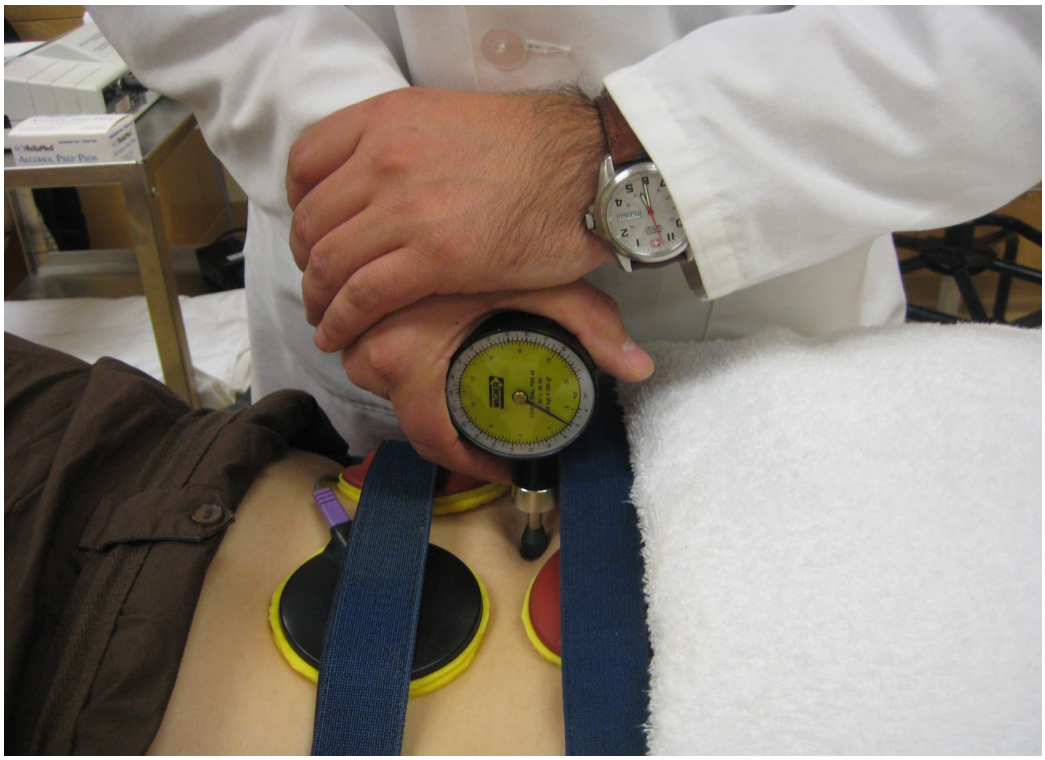

Figure 2. Carbon rubber electrodes placed over lumbar (L1) and sacral (S2) areas. Mechanical algometer applied perpendicularly over the right erector spinae muscle targeted as the central area of stimulation (4 cm to the right of the spinous process of L4).

5.2.3. THERAPISTS AND TRAINING METHODS

Three female trained physical therapists applied the IFC treatments. Their mean age was 35.6 years and their average clinical experience in the management of musculoskeletal disorders was 11.3 years. The therapists were also formally trained in methods of patient-clinician interactions by a clinical psychologist to ensure they were able to create the two different therapeutic contexts (i.e. limited interaction versus enhanced interaction). Therapists were instructed in advance on the scripts for their interactions with the active and sham groups by means of a training manual and by role-playing with simulated patients.[47]

5.2.4. ADHERENCE TO TREATMENT PROTOCOL

Adherence of the clinicians to protocols was based on how closely they followed the established procedure.[47, 49, 50] This was assessed by videotaping all treatment sessions of which 28 (20%) were randomly selected for evaluation. Two research assistants not involved with the trial separately rated each session regarding treatment fidelity using an evaluation form specifically designed for this study.

5.2.5. STUDY PROCEDURE

As presented above, subjects were randomized to receive one single session of one of the following treatments: active IFC in a limited therapeutic encounter, sham IFC in a limited therapeutic encounter, active IFC in an enhanced therapeutic encounter or sham IFC in an enhanced therapeutic encounter.

At the beginning of the treatment session, the treatment procedure was explained to the participants through the use of a standard information sheet. Participants were told that they would receive either the standard electrotherapy treatment for their condition (i.e. active) or a new treatment based on a sub-threshold level of electrical stimulation (i.e. sham) for 30 minutes. General characteristics of the treatments were also provided to the participants.

Later, the participants' personal and demographic data were recorded. In addition, the level of disability (ODI), pain intensity (PI-NRS), and expectations of pain relief (CEQ) were assessed.

Normal skin sensation was tested at the stimulation site (lumbar area). Before conducting the PPT assessment, subjects were instructed in the application of the algometer and given a demonstration. They then underwent a practice test of PPT measurements until the subjects felt they understood the sensation and what they were being asked to do and feel. A trained physiotherapist assessor (JF) measured the PPTs by applying a calibrated mechanical algometer (Wagner Instruments, Greenwich, CT 06836-1217) at a constant rate of force of 1 kg/cm^2/second. The algometer was applied perpendicularly over the right erector spinae muscle, landmarked for reproducibility, 4 cm to the right of the spinous process of L_4 (see Figure 2). The erector spinae muscle was chosen because it has previously been used in clinical [81, 82], and experimental settings [45, 46, 63], excellent intra-examiner reliability has been reported,[63, 83] and normative values are available for this area.[83] The force recorded by the algometer was the minimum amount of pressure that evoked the first sensation of pain.[83, 84] During the procedure, patients were instructed to differentiate the pressure from a feeling of "being pressed" to "initial pain recognition (threshold)." [61] Subjects were asked to say "stop" as soon as they felt a clear sensation of pain, distinct from pressure or discomfort.

PPT measurements were taken on four different occasions during the experimental procedure; M1 (10 min pre-treatment), M2 (time 0 start of treatment), M3 (15 min into treatment), M4 (30 min- end of treatment) (see Figure 3). On each occasion, two consecutive PPT measurements performed 60 seconds apart were collected and averaged for analysis.

During treatment, participants lay in a prone position with the arms relaxed alongside the trunk. The same electrode arrangement was considered for all 4 treatment groups (see Figure 2).

After completing the treatment, pain intensity (PI-NRS) and expectations of pain relief (CEQ) were assessed. At this point, the therapeutic alliance questionnaire of the PRES scale was given to the subject to be completed. In addition, participants were asked whether they felt the treatment was successful. Finally, participants completed the global rating scale.

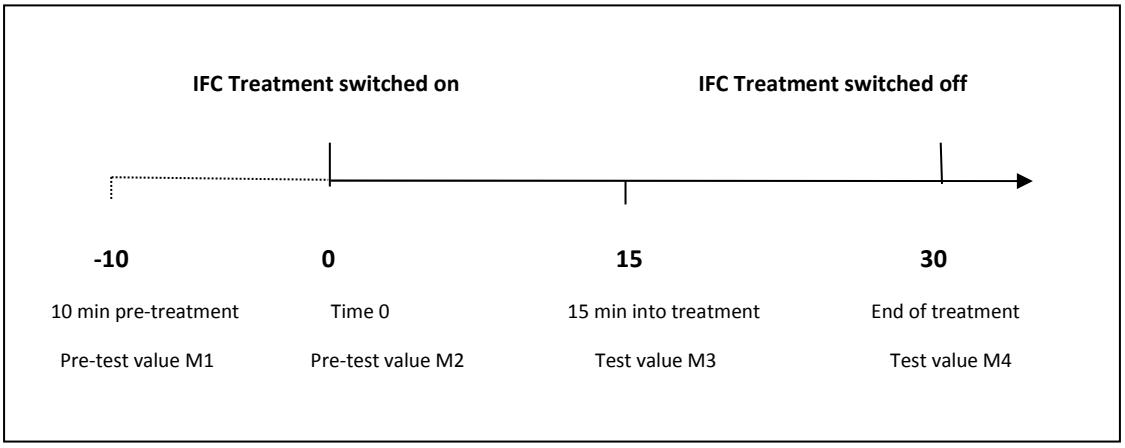

Figure 3. Description of the recordings of pressure pain thresholds (PPT) at different time intervals during the study for the different study groups.

5.2.6. ADEQUACY OF BLINDING

To determine whether or not the active and sham IFC treatments were perceived differently by subjects, the difference in expectancy scores at baseline between the two treatments (i.e. active IFC, sham IFC) were calculated. To prevent cross contamination, participants in the different groups were asked not to talk to each other about the study details during the study period. In addition, after the session

ended, participants were asked to guess the type of the treatment (i.e. active IFC or sham IFC).

5.2.7. OUTCOME MEASURES

Patients were evaluated by a blinded outcome assessor and the timing of outcome assessment was similar in all four groups. Outcomes of interest for assessing the magnitude of the effect for the different treatments applied included the pain intensity numerical rating scale (PI-NRS) and muscle pain sensitivity as measured through pressure pain thresholds (PPT).

Pain intensity

The PI-NRS is a self-reporting measure of pain intensity.[51] The PI-NRS involves asking patients to rate their pain intensity by selecting a number on a horizontally depicted 11-point scale from 0 (no pain) to 10 (worst possible pain).[52] Based on its several advantages (i.e. more responsive, sensitive and easy to administer) over other pain measuring scales, the PI-NRS has been recommended as a core outcome measure in clinical trials of chronic pain treatments. [53, 54] The PI-NRS has been shown to be a reliable and valid measure of pain severity particularly in patients with chronic LBP.[55, 56] The minimal clinically important change for LBP has been reported to range from 1.5 to 3.2 points.[57] Other authors have determined a meaningful clinical change of 2 points from baseline pain scores.[54, 58-60]

Muscle pain sensitivity

Muscle pain sensitivity was evaluated through the PPT, or the minimum pressure that induces pain or discomfort.[61] PPT measurements have been shown to have good or excellent inter-rater ICC values ranging from 0.74 to 0.90 [62] and intra-rater reliability ICC values ranging from 0.75 to 0.99.[63-67] In addition, good values of sensitivity (0.77 to 0.88) and specificity (0.87 to 0.94) for conditions such as myofascial pain and fibromyalgia have been reported.[68, 69] The minimal clinically important change calculated for this outcome has been reported to be ≥ 1.10 $Kg/cm^2/s$ [46, 70]

The therapeutic alliance

The therapeutic alliance between the therapist and the patient was measured by using the working alliance sub-scale of the Pain Rehabilitation Expectations Scale (PRES). The PRES is a self-reported clinical intervention-specific assessment tool developed to measure proxy efficacy, motivation/ expectations, and working alliance for rehabilitation interventions in LBP patients.[71] Accordingly, the PRES encompasses three different sub-scales with 35 items (10 items for proxy efficacy, 14 items for motivation/expectation, and 11 items for working alliance) rated on a 4-point Likert scale ranging from 1 (strongly disagree) to 4 (strongly agree). Scores for the PRES scale range from 0 to 44 (see Appendix 4). Preliminary psychometric results validated the factorial structure of the PRES.[71] In addition, high values of internal consistency for each sub-scale (proxy efficacy α 0.93, motivation/expectations α 0.95, and working alliance sub-scale α 0.96) have been reported.[71]

Level of expectations

Patients were asked to rate their expectations of pain relief using the Credibility and Expectancy Questionnaire (CEQ). The CEQ tool has been widely used in clinical trials in diverse areas such as psychology[72, 73] pharmacology [74] physiotherapy [75], and cognitive-behavioral therapy [76, 77] to determine level of expectations. The CEQ comprises 6- items (2 sets) and two factors (i.e. credibility and expectancy). Items 1 to 3 measure credibility, while items 4 to 6 appraise expectancy. Subjects are asked to rate items on a scale of 1 to 9, with anchors provided for 1 ("not at all), 5 ("somewhat"), and 9 ("very").[78, 79] Thus, for the expectancy variable a minimum score of 3 points and a maximum of 27 points can be obtained. The CEQ is considered to be a valid and reliable[79] tool to measure the expectancy construct.

Global rating scale (GRS)

In rehabilitation disciplines, the patient's perspective is highly valued. The assessment of clinical significance from the participant's perspective was assessed through the GRS. The GRS is one of the most commonly tools used in health research.[80] This scale can be used to rate the magnitude of change they have experienced in a specific dimension (i.e. pain). Patients respond by identifying the degree of change on a 15-point Likert scale, with -7= a very great deal worse, 0= about the same, and +7= a very great deal better [80] Changes of ±1-3 represent small changes, ± 4-5 moderate changes, and ± 6-7 large changes.

All measurements included under the four treatment conditions (i.e. group 1 to group 4) were performed by the same-trained investigator who was blind to the

type of IFC treatment applied and to the statistical analysis of data. Participants were blind to intervention status. Treatment and outcome measurements were conducted in a quiet, isolated treatment area, free of outside distractions.

5.3. STATISTICAL ANALYSIS

An a priori sample size of 116 participants (i.e. a minimum of 29 per group) was calculated for a four group MANOVA, with repeated measures to detect a change of ≥ 2 points on the PI-NRS with a power of 0.80, $\alpha = 0.05$, and a moderate effect size 0.75 using established statistical guidelines.[85]

Baseline participant's characteristics for the four treatment groups were compared using independent t-tests for continuous variables. A two-way repeated measures MANOVA was used as the main test to evaluate the differences in PI-NRS and PPT's among treatment groups. Pairwise comparisons using Bonferroni's post hoc test were used to determine whether specific differences between each of the groups existed. In addition, in order to determine if different therapists influenced the way that patients responded to the treatments, a 2 way MANOVA analysis (2 factors: group treatment and therapist) on pain and PPT outcomes was performed. The level of significance was set at $\alpha = 0.05$.

Calculation of the effect size (Cohen d)[86]was included to determine the magnitude of the therapeutic effect and the clinical significance for both main outcomes (i.e. pain intensity and muscle pain sensitivity) among treatment groups. Clinical significance from the participant's perspective was assessed through the global

rating scale. The MID for PPT and pain intensity were calculated from the GRS following the guidelines established by Guyatt et al.[80] SPSS version 17.0 program was used to perform the statistical analysis. The level of significance was set at $\alpha = 0.05$. The analyst conducting the analysis was blinded to treatment allocation since an external research assistant codified the data to be analyzed.

5.4. RESULTS

5.4.1. SUBJECTS

A total of 117 participants with chronic LBP were enrolled. Their mean age was 30 years (SD= 6.8, range = 19- 65 years), mean height was 1.69cm (SD= 8.2), and mean weight was 67 kg (SD= 14.4). None of the 117 participants withdrew, and complete data was available on all 117. As indicated in Table 1, baseline demographic, body weight, height, pain intensity, pain chronicity, and level of expectations among groups were not significantly different ($p>0.05$).

Table 1. Baseline variables for the four treatment groups

Characteristics	AL (n= 30)	SL (n= 29)	AE (n=29)	SE (n=29)	P value
Age	30.5 (10.26)	30.3 (11.22)	29.7 (11.33)	29.8 (10.78)	0.991
Height (cm)	170.9 (9.53)	168.2 (10.11)	169.1 (9.41)	169.4 (10.13)	0.769
Weight (kg)	69.6 (18.64)	66.6 (11.99)	67.1 (13.28)	65.3 (18.64)	0.695
Sex	Female 18 (60%)	Female 17 (58.6%)	Female 19 (65.5%)	Female 17 (58.6%)	
	Male 12 (40%)	Male 12 (41.4%)	Male 10 (34.5%)	Male 12 (41.4%)	
PI-NRS	4.01 (0.91)	4.09 (0.10)	4.03 (0.92)	4.10 (0.12)	0.986
CEQ initial	15.6 (2.69)	15.2 (4.51)	15 (2.73)	16 (4.80)	0.898
Pain duration (months)	45.3 (56.76)	51.1 (38.19)	51.21 (38.30)	47.28 (87.29)	0.974

Data are presented as mean and standard deviation. Significant differences $P < 0.05$
AL= active limited, SL= sham limited, AE= active enhanced, SE= sham enhanced. PI- NRS= pain intensity numerical rating scale, CEQ= credibility expectancy questionnaire score before treatment.

5.4.2. DIFFERENCES BEFORE-AFTER ON PPT AND PAIN INTENSITY BY GROUPS

MANOVA testing determined that there were statistically significant differences between groups on the mean change (before-after) of PPTs and pain intensity scores ($p< 0.05$). Results of the multiple comparisons between groups using the Bonferroni post hoc test for PPTs and pain intensity are displayed in Table 2.

Pain intensity

Mean differences (before-after) in pain intensity (PI-NRS) were 18.3 mm (95% CI 14.3 to 20.3), 10.3 mm (95% CI 6.6 to 12.7), 31.3 mm (95% CI 27.2 to 33.3), and 22.2 mm (95% CI 18.9 to 25.0), for the groups AL, SL, AE, and SE respectively. Percentages of pain reduction were 45.5%, 24.5%, 77%, and 54.5% for the groups AL, SL, AE, and SE respectively (see Table 3 and Figure 4).

Muscle pain sensitivity

Mean differences (before-after) in PPTs were 1.2 kg (95% CI 0.7 to 1.6), 0.3 kg (95% CI 0.2 to 0.8), 2.0 kg (95% CI 1.6 to 2.5), and 1.7 kg (95% CI 1.3 to 2.1), for the groups AL, SL, AE, and SE respectively. Percentages of increased pain thresholds were 32.6%, 10.5%, 51.5%, and 40.0% for the groups AL, SL, AE, and SE respectively (see Table 3 and Figure 5).

Table 2. Pairwise comparisons for muscle pain sensitivity (PPT) and pain intensity

Time	(I) group	(J) group	Mean difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for difference [a]	
						Lower Boundary	Upper Boundary
PPT	AL	SL	0.816	0.308	0.055	-0.010	1.642
		AE	-0.856*	0.308	0.038	-1.682	-0.030
		SE	-0.525	0.308	0.543	-1.351	0.301
	SL	AL	-0.816	0.308	0.055	-1.642	0.010
		AE	-1.672*	0.310	0.000	-2.505	-0.839
		SE	-1.341*	0.310	0.000	-2.174	-0.508
	AE	AL	0.856*	0.308	0.308	0.030	1.682
		SL	1.672*	0.310	0.000	0.839	2.505
		SE	0.331	0.310	1.000	-0.502	1.164
	SE	AL	0.525	0.308	0.308	-0.301	1.351
		SL	1.341*	0.310	0.000	0.508	2.174
		AE	-0.331	0.310	1.000	-1.164	0.502
PAIN	AL	SL	7.623*	2.166	0.004	1.806	13.440
		AE	-12.949*	2.166	0.000	-18.766	-7.132
		SE	-4.673	2.166	0.199	-10.491	1.144
	SL	AL	-7.623*	2.166	0.004	-13.440	-1.806
		AE	-20.572*	2.184	0.000	-26.439	-14.706
		SE	-12.297*	2.184	0.000	-18.163	-6.430
	AE	AL	12.949*	2.166	0.000	7.132	18.766
		SL	20.572*	2.184	0.000	14.706	26.439
		SE	8.276*	2.184	0.001	2.410	14.142
	SE	AL	4.673	2.166	0.199	-1.144	10.491
		SL	12.297*	2.184	0.000	6.430	18.163
		AE	-8.276*	2.184	0.001	-14.142	-2.410

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni

*. The mean difference is significant at the 0.05 level

AL= active limited, SL= sham limited, AE= active enhanced, SE= sham enhanced

Table 3. Mean differences (baseline and post-treatment) in muscle pain sensitivity (PPT) in kg/cm^2/second and pain intensity scores (PI-NRS) for the treatment groups (mean ± SD.

Outcome measure	Active Limited (n=30)	Sham Limited (n= 29)	Active Enhanced (n= 29)	Sham Enhanced (n= 29)
Pain intensity (PI-NRS)				
Baseline	4.01 (0.91)	4.09 (1.0)	4.03 (0.92)	4.10 (1.29)
Post-treatment	2.18 (1.17)	3.06 (1.27)	0.89 (0.98)	1.88 (1.44)
Difference	1.83 (0.85)	1.03 (0.65)	3.13 (0.97)*	2.22 (0.75)*
% of change (pain reduction)	45.6	24.5	77.4	54.5
Muscle Pain Sensitivity (PPT)				
Baseline	3.89 (1.8)	3.76 (1.8)	4.11 (1.8)	4.5 (2.3)
Post-treatment	5.15 (2.6)	4.16 (1.6)	6.21 (2.6)	6.3 (2.8)
Difference	1.25 (1.3)*	0.39 (0.9)	2.09 (1.1)*	1.75 (1.3)*
% of change (increased PPT)	32.6	10.5	51.5	40.0

* Indicates findings were clinically important according to indexes based on distribution (i.e. MID [Minimally Important Difference], SEM [Standard Error of Measurement]) reported in the literature.

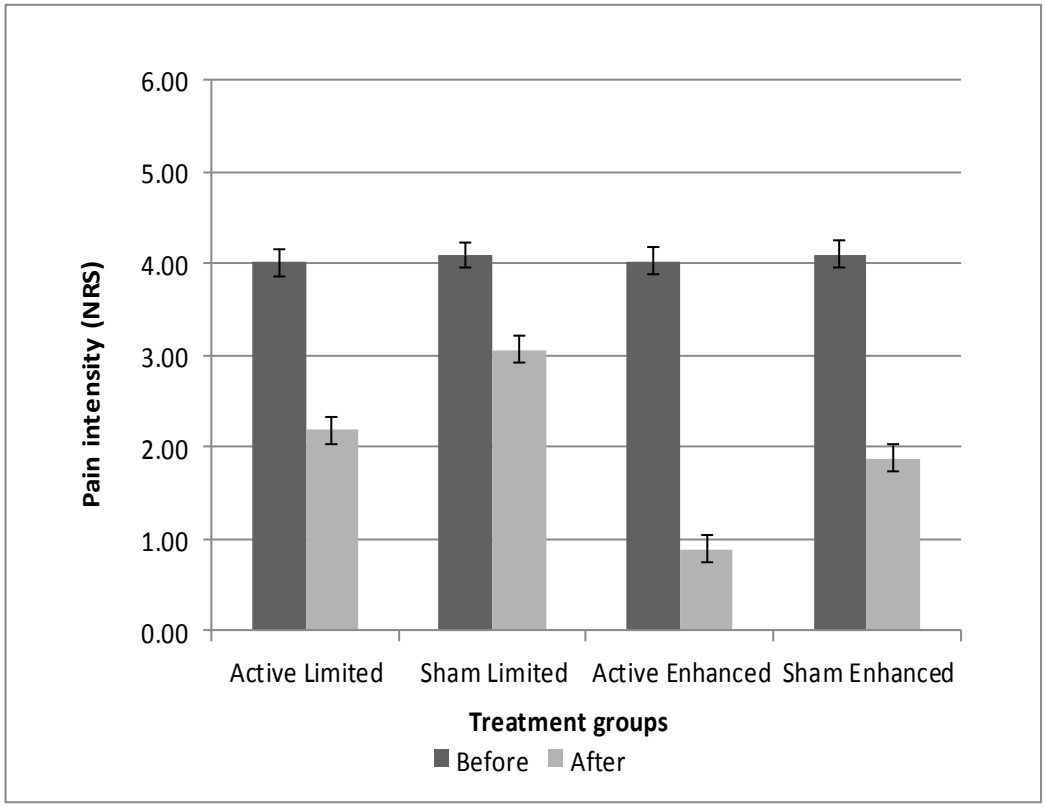

Figure 4. Mean differences (before – after) in pain intensity scores (PI-NRS) for the four treatment condition

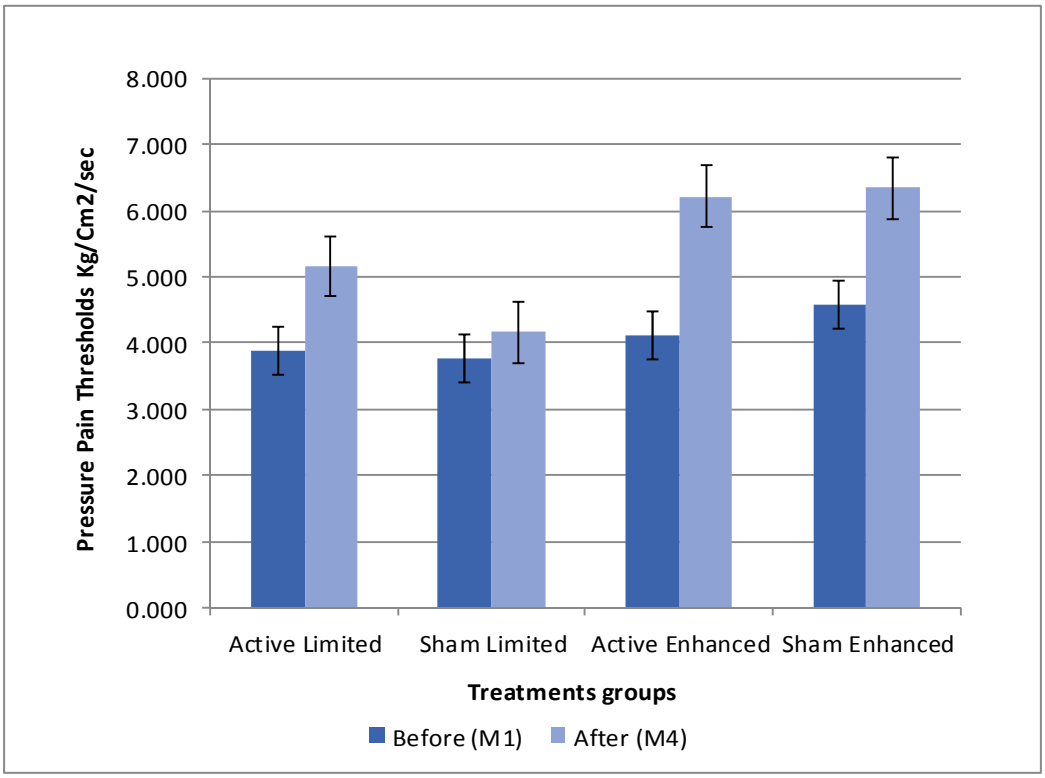

Figure 5. Mean PPTs (Kg/cm^2/sec) before (M1= -10 min) and after (M4 = 30 min) for the four IFC treatments. Results are shown as mean ± SEM.

5.4.3. DIFFERENCES AT DIFFERENT TIME POINTS DURING THE EXPERIMENTAL PROCEDURE (M1-M4) ON PPT AND PAIN INTENSITY BY GROUPS

In addition, a two-way ANOVA mixed design with repeated measures found a significant main effect on time ($p< 0.01$), and a significant interaction between time and group ($p<0.01$) for PPT measures. Results of the multiple comparisons between group and times of the trial using the Bonferroni post hoc test for PPTs showed significant differences at 15 minutes between SE and SL groups ($p= 0.03$,

95% CI 0.1 to 3.4), at 30 minutes between AE and SL (p= 0.01, 95% CI 0.2 to 3.0), and at 30 minutes between SE and SL (p< 0.01 (95% CI 0.4 to 3.9).

5.4.4. THERAPIST EFFECT

A 2 way MANOVA test determined that there was no significant differences between therapist (p=0.18) or any interaction between therapist and groups (p=0.10), either for pain or for PPT outcomes (Figures 6 and 7). In other words, therapists were similar in providing the treatment and did not have an influence in the way that patients responded to different treatments.

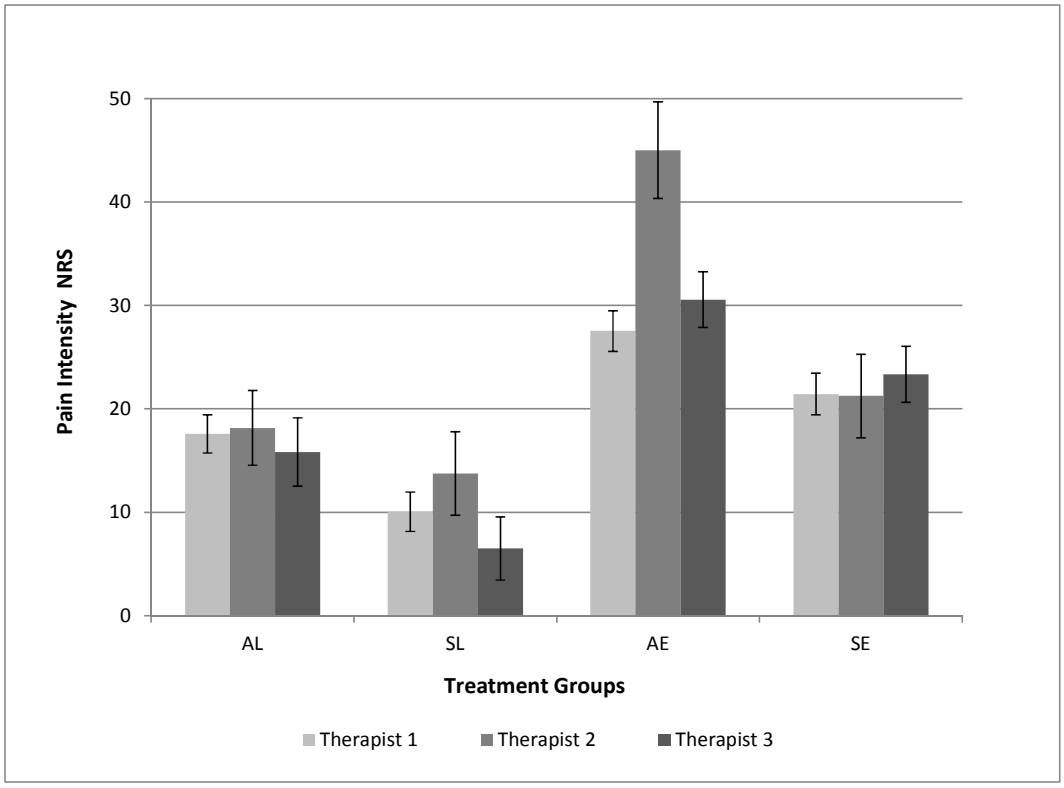

Figure 6. Therapist effect by treatment group on pain intensity (PI-NRS scores).Results are shown as mean ± SEM.

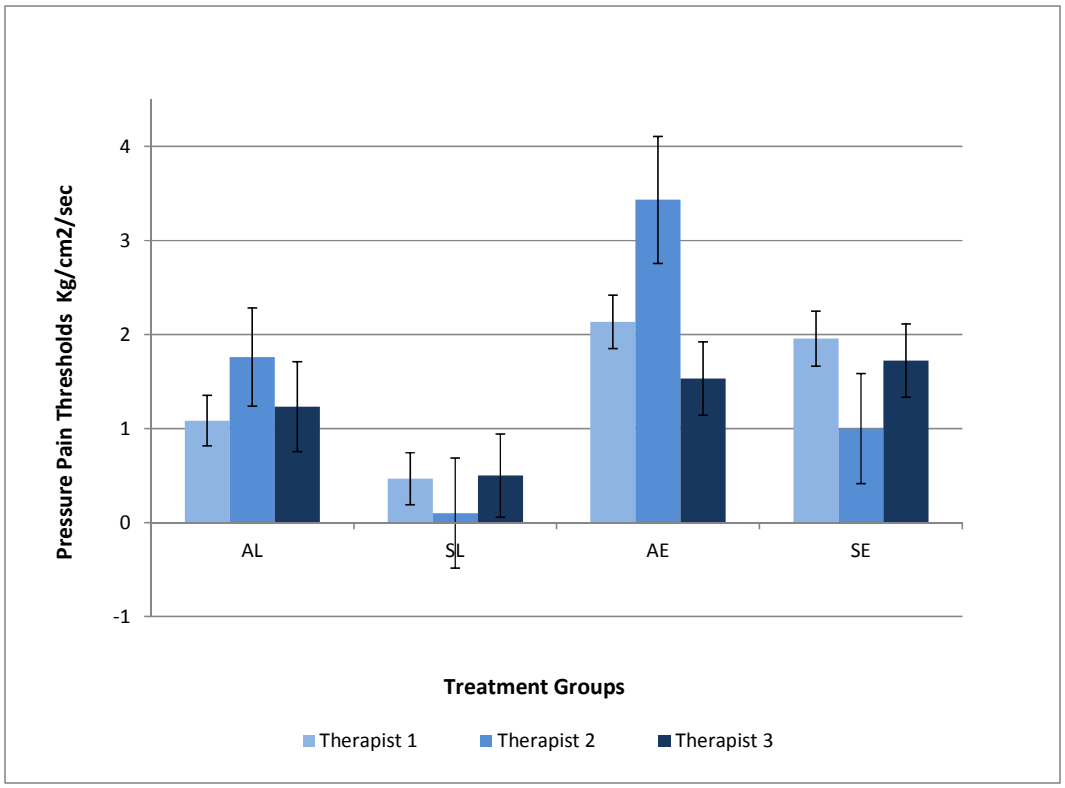

Figure 7.Therapist effect by treatment group on PPTs (Kg/cm^2/sec). Results are shown as mean ± SEM.

5.4.5. THERAPEUTIC ALLIANCE SCORES ACROSS GROUPS

Scores for the therapeutic alliance (PRES) assessed at the end of the session were 34.3 (SD= 4.4), 30.6 (SD= 5.5), 43.0 (SD= 1.8), and 42.0 (SD= 2.6) for the AL, SL, AE, and SE groups respectively. Scores between the two enhanced groups (AE, SE) were not significantly different ($p= 1.0$). Scores between active limited and enhanced groups (AL, AE), and sham limited and enhanced groups (SL, SE) were significantly different ($p< 0.00$).

5.4.6. CLINICAL IMPORTANCE

Pain intensity

Group differences for pain intensity (PI-NRS) between baseline and at 30 minutes of treatment, identified for groups AE (31.4 mm) and SE (22.2 mm) exceeded suggested values for the smallest clinically meaningful differences.[54, 58-60] Large effect sizes (Cohen d) between baseline and at 30 minutes of treatment were found for all groups, being d=0.86, d= 1.60, d= 1.73, and d= 3.26 for the groups SL, SE, AL, and AE respectively. In addition, clinically important effect size differences were found between the SL and AE groups (d= -2.51), SL and SE groups (d= -1.73), AL and AE groups (d= -1.36), AE and SE groups (d= 1.0), and AL and SL groups (d= 0.89).

Muscle pain sensitivity

Groups differences for muscle pain sensitivity (PPT) between baseline and at 30 minutes of treatment for groups AL (1.2 kg/cm^2), AE (2.0 kg/cm^2), and SE (1.7 kg/cm^2), reached values deemed to be clinically relevant.[46, 70] A large effect size (Cohen d) was found for the AE group (d=0.9), moderate effect sizes were observed for the SE (d= 0.6) and AL group (d= 0.5), and a small effect size was observed for the SL group (d= 0.2). Also, clinically important effect size differences were found between the SL and AE groups (d= -0.9) and SL and SE groups (d= -0.9).

Global rating scale

Average change in the global rating scale reported by participants was 4 points, 2 points, 5 points, and 4 points for the AL, SL, AE and SE groups respectively. Ninety percent of participants in the AE group perceived the change as moderate (i.e. ± 4-5 points) while this change was reported in less than 5% of participants in the SL group. Average pain intensity considered minimally important for participants was calculated to be 12 mm. Therefore, only 22.5% of participants felt that the treatment they received was unsuccessful for controlling their pain. In addition, the average PPT considered minimally important for participants was calculated to be 1.05kg/cm^2/seconds. Accordingly, 39% of participants felt the intervention was not effective for increasing their pain thresholds.

5.4.7. BLINDING ASSESSMENT

Expectations at baseline among the 4 treatment groups (i.e. AL, SL, AE, SE) were not significantly different (p= 0.90, see Table 1). This means that the expectations of the groups were similar and participants (before they received treatment) perceived active and sham treatments as comparable.

In addition, when participants were asked at the end of the session to guess the type of treatment (i.e. active or sham IFC), 87% (n= 25) of participants in the SL, and 97% (n=28) in the SE group thought they had been treated with an active intervention. In other words, only 8% (n=5) of all participants in both sham groups (n=58) correctly guessed that they had not received an active treatment.

This provides some evidence that the blinding procedures were adequate and that both the active and the sham treatments were perceived equally by the participants. No one in the active groups (AL, AE) thought they received a sham intervention.

5.4.8. ADHERENCE TREATMENT PROTOCOL

Evaluation of videotaped interactions indicated that 86% of the sessions evaluated were rated as adherent to the protocol by 2 research assistants unconnected with the study. Reliability on these ratings between the raters was considered excellent (ICC=0.95, 95% CI 0.8 to 0.9; $p<0.01$). The 14% of non-adherent sessions included only sessions for the enhanced groups (AE, SE). The fault observed for the therapists in these sessions was the no inclusion of words of encouragement to the participant at the end of the treatment.

5.4.9. ADVERSE EFFECTS

An important safety feature when applying electrotherapy modalities is the report of adverse effects. Reporting adverse effects must be included as a mandatory aspect not only for the safety of patients, but also for professional integrity. Although IFC is considered a safe modality, its application has been associated with local adverse effects such as blisters, burns, bruising and swelling.[87,88] In this study, two participants (one female receiving active IFC in a limited interaction, and one male receiving sham IFC in a limited interaction) reported an increase in

their pain with no apparent reason after receiving the IFC treatment session. No other adverse effects were reported or observed among participants.

5.5. DISCUSSION

This study examined the impact of therapeutic alliance on clinical outcomes in patients with nonspecific chronic LBP. The most striking result of this randomized, double-blind, controlled study was the relevant effect of the enhanced therapeutic context on pain modulation. As hypothesized, more beneficial outcomes were found for patients on the enhanced therapeutic alliance groups (active enhanced and sham enhanced) when compared with the limited interaction groups (active limited and sham limited).

5.5.1. THERAPEUTIC ALLIANCE IN PHYSIOTHERAPY

The results of this present study suggest that the therapeutic context, in which the intervention (i.e. IFC) was applied may be more relevant than the intervention itself. The therapeutic alliance (i.e. nonspecific treatment effect) seems to be more important than the specific effect of the IFC in reducing pain intensity and muscle pain sensitivity.

Since this is the first study looking at the effect of manipulation of the TA in chronic pain receiving a physiotherapy intervention, direct comparisons cannot be made. However, our results are in line with a recent study [99] that confirmed that a

supportive patient-practitioner relationship is the most potent component of placebo effects in the management of patients with irritable bowel syndrome. In this study, the magnitude of the effect for an augmented interaction (i.e. 45 minutes' duration including supportive, warm, active listening behaviors) between the practitioner and the patient was not only statistically but also clinically significant for pain, symptom severity, and quality of life outcomes compared with limited interaction (i.e. 5 minutes) and the natural history of the condition (waiting list control group). Although methodological differences are present between both studies, some similarities such as the intervention protocol and the use of subjective outcome measures makes the comparison between these two RCTs worth considering.

In medicine, a recent body of literature has shed light on the importance of nonspecific effects of the doctor-patient relationship and communication styles on outcome of treatment.[100-102] Similar to medicine, in physiotherapy, it is conceivable that the patients' differences in treatment responsiveness are likely related to the therapist's interpersonal skills rather than the appropriateness of the treatment technique. This notion may have some support considering the nature of therapeutic interventions in which features such as touch, care, and attention play a relevant role. Thus, physiotherapy encounters typically exhibit high levels of patient-clinician interaction. Since the placebo effect is directly associated with the degree of such interaction, the therapist could be a major contributor to the placebo response in physiotherapy.[103] The results of recent systematic reviews and meta-analyses about common non-pharmacological interventions used by

physiotherapists to treat chronic LBP have shown similar and modest short-term benefit, but little long-term benefit. [104, 105] It is plausible that these limited results occurred because contextual factors (e.g. expectations, TA) inherent to clinical encounters were not encouraged during the application of interventions during these controlled trials. In clinical settings, it is possible that treatments applied in a neutral or in a 'business-like manner' (i.e. the contextual factors are not enhanced) may translate into less than optimal clinical outcomes.

5.5.2. MAGNITUDE OF THE EFFECT

The results of the study showed a clear dose-response effect, where the largest beneficial effect occurred in the active IFC group with enhanced TA (AE) and the smallest effect was displayed by the sham IFC in a limited TA (SL). These findings met our hypotheses, however, the magnitude of the effect in the AE group was larger than we had anticipated. On average, participants in the AE group had decreased pain intensity by 3.1 points on the PI-NRS. In addition, they increased their PPTs by 2.09 $Kg/cm^2/s$. These values largely exceeded what is considered a clinically meaningful change for these outcomes. [46, 70] These differences also correspond to the large effect sizes calculated for pain (d= 3.26) and PPT (d= 0.93) outcomes in our sample.

On the other hand, clinical outcomes for the participants in the SL group showed the smallest effect. Participants in this group reported a decrease in pain of only 1.0 point on the PI-NRS and an increase in PPT of 0.39 $Kg/cm^2/s$. These values are not considered clinically meaningful. Interestingly, the sham IFC with an

enhanced TA (SE) displayed better results than the active IFC with a limited TA (AL). Change in pain intensity on the PI-NRS for the SE group was 22.2 points and 18.3 points for the AL group. Accordingly, changes in PPTs were 1.75 $Kg/cm^2/s$ and 1.25 $Kg/cm^2/s$ for the SE and AL groups, respectively. Although differences were not significantly different between groups, whether or not a sham application (i.e. no active ingredient) in an enhanced TA is better than an active intervention (i.e. active ingredient included) in a limited TA would be worthwhile exploring further.

Analysis of clinical relevance from the patient's perspective showed that most of participants rated their change in pain after the treatment as clinically meaningful. Thus, average scores in the GRS reported were 5 points, 4 points, and 4 points for the AE group, SE group and AL groups respectively. This contrasted with the perception of change in pain rated by the participants in the SL group where the average score in the GRS was 2 points, representing a small change.

5.5.3. MECHANISMS

Some mechanisms have been proposed to explain the positive effects of the TA on treatment outcomes. Recently, evidence has shed light on the neurobiology of the clinician-patient relationship and the mechanisms of how appropriate words from the clinician can induce meaningful changes in neural activity leading to the activation of the endogenous opioid system, biological changes and improved pain outcomes.[23, 47, 89, 90] For example, it has been shown that when the clinician-

patient relationship is absent, the magnitude of the analgesic response is reduced.[16, 91-93] Elimination of the TA negatively influences pain outcomes, possibly due to a reduced activation of opioid mechanisms in patients in the absence of the doctor or nurse during the clinical procedure.[94]

Also, personal characteristics of clinicians can influence treatment outcomes either positively or negatively. Some potential behavioral styles may favor or inhibit placebo responses. For example, the clinician, by listening, sending appropriate messages, and physically contacting the patient during the clinical examination may induce a strong placebo effect, whereas inappropriate comments may exacerbate the symptoms.[94] Other therapeutic variables that enhance placebo responses include the amount of time the clinician spends with patients and a warm emphatic interaction [47, 49]

In this study, physiotherapists in the enhanced groups were present for the whole treatment session, and they also included behaviors such as active listening (i.e. repeating patient's words, asking for clarifications), empathy (such as saying: "I can understand how difficult CLBP must be for you"), and few words of encouragement (i.e. I do understand that at times, chronic pain can be something that is beyond your control… Whatever happens, try to be patient with yourself and look forward to good things that are ahead for you).

The interaction between practitioner and patient has been considered central in determining outcome in back pain and neck pain.[95, 96] It is plausible that the reduced scores in pain and the increased pain thresholds exhibited by the patients

in both enhanced groups could be the result of opioid activation as a consequence of the increased attention given by the physiotherapists. In addition, the enhanced communication skills, and the concerned optimism exhibited about the patient by the physiotherapist during the treatment session could potentially explain these results. Finally, available data suggest that the placebo-associated improvement is strongly influenced by the patient's awareness of the procedure and depends on the invasiveness of the procedure; elaborate rituals can produce effects that are greater than a simple pill ingestion.[97, 98] Thus, the application of a highly technologically impressive piece of equipment such as an IFC machine may have resulted in a highly evocative and therapeutically potent agent for the patients in our study.

5.5.4. THERAPIST EFFECTS

In this study we did not find significant differences between the therapists and interaction between therapist and groups on clinical outcomes. This demonstrated that individual differences (i.e. personality) among therapists did not influence the placebo response. This finding suggests that when different therapists adhere, as shown by our study, a highly scripted and standardized treatment protocol, their personality attributes may not have an influence in the way that patients responded to treatments.

5.5.5. STRENGTHS AND LIMITATIONS OF THE STUDY

To our knowledge, this is the first randomized controlled study aimed at exploring the effects of manipulating the TA in physiotherapy treatment of chronic pain. The testing protocol was standardized and conducted in our lab to minimize bias, but this made the environment somewhat different that routine clinical practice. There were many characteristics of the design that strengthen the results. Our trial had high internal validity as shown by adequate randomization, concealed allocation, baseline comparability among groups, and evidence of effective blinding of the research team and participants. Experienced clinicians delivered the interventions, in accordance with a highly standardized study protocol designed to deliver different therapeutic contexts. We also excluded persons with previous experience in IFC.

While the results of this study are encouraging, any inference from this study needs to be tempered due some limitations. First, the positive effects shown in the enhanced groups (i.e. AE, SE) could be due to the possibility that patients in these groups were more willing to please the therapist compared with the patients in the limited groups (i.e. selection bias). Second, since we did not include a "no treatment" control group, the results of this study might be under scrutiny. It is probable that participants in the enhanced groups could have had an improvement in their pain due to natural variability in pain levels alone. However, it is likely that this confounder (pain variability) would have equally affected all groups and thus would not account for the differences in the analgesic effect observed across groups. In addition, this study involved just one session of treatment, therefore

elements such as the natural history of LBP were not likely to have compromised our findings. Third, our study protocol aimed to test the immediate effect of the therapeutic alliance. Therefore, there is a need to determine if these reported benefits could be sustained in the longer term. Thus, future research is needed to overcome these limitations and expand the analysis of the existing evidence regarding the effects of TA as another therapeutic agent within clinical practice.

5.5.6. IMPLICATIONS FOR PRACTICE

The results of this study provide an important clinical contribution to the area of physiotherapy and the management of chronic musculoskeletal conditions. In this study, the combination of active IFC in an enhanced TA displayed the most significant and clinically meaningful therapeutic benefits. These results call for a more in-depth consideration of contextual factors when delivering therapy. Physiotherapists should consider optimizing the psychosocial context in the clinical management of chronic pain conditions. This is especially important in conditions (e.g. chronic LBP) where the effects of specific physiotherapy interventions have been shown to be of modest value in controlled trials. In addition, since chronic conditions demand considerable commitment by patients when implementing treatment regimes, a strong alliance between the therapist and the patient is essential to achieve patient compliance. Ideally, physiotherapists should combine the power of modern technologies, better therapeutic approaches, and the therapeutic value of the placebo effect, specifically including an enhanced TA, in their treatments. In other words, the TA may be considered as another

therapeutic agent. Therefore, physiotherapists' awareness of this factor when delivering their interventions could lead to better outcomes.

5.6. CONCLUSION

This randomized clinical trial showed the beneficial and clinically relevant effects of an enhanced therapeutic encounter when treating patients with chronic LBP. Results support efforts to foster enhanced alliance between patients and providers when delivering physiotherapy interventions for people with chronic pain. Potentially, treatment effects depend more on nonspecific factors of care – such as therapeutic alliance - rather than specific effects of physiotherapy treatments. Further research on the role of nonspecific effects in physiotherapy practice is warranted.

5.7. ACKNOWLEDGEMENTS

Jorge Fuentes is supported by the University of Alberta, through the Dissertation Fellowship Award. This project was funded by the Physiotherapy Foundation of Canada (PFC) through the Ortho Canada Research Award, and the Department of Physical Therapy, University of Alberta through a Thesis Research Operating Grant Program.

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CHAPTER 6

CONTRIBUTORS FOR THE PLACEBO MEDIATED ANALGESIA IN CHRONIC LOW BACK PAIN

Background: The analysis of the effectiveness of the placebo effect and placebo analgesia is enriched when the placebo determinants are taken into account. Despite some consensus on the physiologic mechanisms underlying the placebo effect, there is less agreement on the variables associated with the placebo analgesia response.

Objective: To explore the determinants of placebo response in participants with chronic low back pain (LBP) receiving physiotherapy.

Methods: Data was analyzed from a randomized controlled trial designed to determine the impact of the therapeutic alliance on pain intensity (PI-NRS) and muscle pain sensitivity (PPT) among participants with chronic LBP. In this study, participants were randomized to receive either a single session of sham interferential current therapy (IFC) in a limited alliance (n=29) or a single sham IFC session with an enhanced alliance (n=29). Three physiotherapists applied the treatments. Potential placebo determinants included personal characteristics (i.e. age, gender), psychosocial variables (i.e. expectancies, therapeutic alliance), and condition-related factors (i.e. pain intensity, pain duration, muscle pain sensitivity, and level of disability). Placebo response was defined as a change in pain intensity in a participant as a result of the application of the sham IFC procedure.

Analysis: Multiple logistic regression was used to identify potential determinants of a placebo response.

Results: The level of alliance (odds ratio 1.22; 95 CI (1.08 to 1.38); $p < 0.01$) and pain duration (odds ratio 0.96; 95 CI (0.93 to 0.99); $p < 0.01$) were the only two factors significantly associated with placebo response. Participants in the enhanced group had an increase in the alliance by 11 points compared to the limited group. This was interpreted as approximately 8 times higher likelihood of being a placebo responder compared to the limited group.

Conclusion: A high level of alliance between patient and therapist and lower pain duration were positively associated with the placebo analgesia response in participants with chronic LBP. This study highlights the power of the alliance and suggests that the quality of the interaction is not only a major factor associated with the placebo response but also considerably influences the size of placebo effect in patients with chronic LBP. These findings have implications for future research in physiotherapy helping to characterize which patients may be placebo responders.

6.1. INTRODUCTION

There is accumulating evidence from different methodological approaches (i.e. clinical and laboratory) that the placebo is a robust psychobiological effect attributable to an overall therapeutic context. [1,2,3-9,10-12] Behavioral [1,2], psychophysiological[3-9], and neuroimaging [12,11,10] results have largely contributed to accepting a placebo response as a genuine psychological and neurophysiological phenomenon with important implications for clinical research and medical care.

While the mechanisms of placebo analgesia (e.g. expectancies, conditioning, observational learning) have become increasingly articulated, very little work has been published addressing factors associated with this phenomenon. Identification of factors or variables that can contribute to the placebo analgesia response would help identify patients likely to be placebo responders. The analysis of the effectiveness of the placebo response and placebo analgesia is enriched when placebo determinants are taken into account.[13] Moreover, predicting the probability of an individual reacting to placebo in physiotherapy could have major implications for improving the design and efficacy of clinical trials, allowing more precise entry criteria into trials. A challenge is to identify the factors that could influence the placebo or the therapeutic contextual response in patients suffering from chronic musculoskeletal pain, especially chronic low back pain (LBP).

Some research has attempted to identify factors associated with a placebo response.[14-18] Although gender differences may help explain the variability in the

magnitude of placebo response,[14] this issue has often been overlooked when discussing and reporting results. In addition, the current evidence about the role of gender as a contributor of placebo analgesia is represented by only a limited number of clinical studies.[15, 16] For example, no gender differences in placebo analgesia have been reported in acute clinical pain.[15, 16] No studies have examined the association of gender on placebo response in chronic painful conditions. In addition, although a significant placebo effect has been reported among older patients with depression,[17]and Parkinson's disease,[18] the role of age as a contributor to placebo response in musculoskeletal pain is unclear.

Despite some direct associations reported between the baseline level of pain intensity and the magnitude of the placebo response in osteoarthritis,[19] data about the contribution of this factor as well as duration of pain as determinants for the placebo physiotherapy response in patients with chronic LBP is still absent. Disability is also a common feature of LBP. [20, 21] The extent to which the level of disability can influence the placebo response is not well understood. For example, to date no association has been confirmed between levels of disability and placebo physiotherapy analgesia in patients with chronic pain. Considering the high prevalence of disability in patients with chronic LBP, it is important to determine whether or not this factor influences the placebo response in patients receiving physiotherapy interventions.

While some evidence also exists regarding the importance of some specific psychosocial attributes, such as expectancies of recovery as a predictor of clinical outcomes in the rehabilitation of LBP, [22-24] little is known about whether or not

this factor contributes to placebo analgesia in the same clinical condition. Consistent clinical and experimental evidence supports the association of expectations in the placebo response. [6, 8, 9, 25, 26] However, with LBP this pattern is not that consistent. For example, two recent studies [25, 27] reached dissimilar conclusions about the effect of patients' expectations and the ability to be associated with the placebo response. Therefore, data about the contribution of this factor as a determinant for the placebo response in these patients is still debatable.

Contextual factors such as the therapeutic alliance (TA), or the positive social connection between the patient and the therapist,[28] have also been reported as positively associated with treatment outcomes in psychotherapy and medicine.[29-32] Although these disciplines include a high interaction with the patient, the characteristics of the patient population and interventions differ from physiotherapy. Therefore, it is of great importance to determine the role of the TA as a potential predictor of treatment outcome as well as a contributor to the placebo response in physiotherapy. Most therapies are rich in cues and rituals.[33] Physiotherapy, in particular, encompasses a high degree of therapist-patient relationship, expectancies and other contextual factors. These features should be investigated to determine their impact and contribution to placebo analgesia in patients with chronic LBP receiving physiotherapy.

In this study we sought to determine whether personal characteristics (i.e. age, gender), psychosocial variables (i.e. expectancies, therapeutic alliance), and/or condition-related factors (i.e. pain intensity, pain duration, muscle pain sensitivity

and disability) were associated with the placebo response. The selection of these variables was based on a review of factors influencing chronic pain treatment outcomes[34] and the clinical relevance of such attributes as possible contributors to the placebo response in patients with chronic LBP receiving physiotherapy treatment. We hypothesised that female gender, greater age, enhanced TA, high expectations of pain relief, greater pain duration, moderate baseline pain intensity, high baseline muscle pain sensitivity and a moderate level of disability would be positively associated with the placebo response in patients with chronic LBP.

6.2. METHODS

6.2.1. STUDY DESIGN

This study involved a secondary analysis of data generated during a double-blind randomized study including 117 participants with chronic LBP. A randomization sequence stratified by gender was computer-generated (http://www.randomization.com) by a research assistant not involved in patient recruitment and evaluation. Eligible participants were allocated to the treatment groups by a physiotherapist who opened the next available sequentially numbered opaque and sealed envelope prior to each treatment session.

The original study involved participants who were randomly divided into 4 groups: active limited (AL) (n=30) included the application of active interferential current (IFC) combined with a limited TA, sham limited (SL) (n=29) included the application of sham IFC combined with a limited TA, active enhanced (AE)

(n=29) included the application of active IFC combined with an enhanced TA, and sham enhanced (SE) (n=29) included the application of sham IFC combined with an enhanced TA. Because this present study aimed to evaluate variables associated with the placebo effect, only the results for the participants in both sham groups were included in this analysis (total n = 58)

The participants assigned to the sham groups received an identical single 30-minute session of treatment. During the sham application, the investigator's instructions were as follows: "today I am going to apply a new treatment called therapeutic sub-threshold current…since the level of stimulation is sub-threshold, you might not be able to feel it beneath the electrodes.[35, 36]

The limited therapeutic alliance included about 5 minutes of interaction between therapists and participant during which the therapist introduced herself and explained the purpose of the treatment. [37]

The enhanced therapeutic interaction included behaviors such as active listening, empathy, and encouragement [37] This intervention model aimed to create an optimal patient-clinician relationship.[37, 38]

6.2.2. PARTICIPANTS

The study was conducted in the sports physical therapy laboratory of the Faculty of Rehabilitation Medicine at the University of Alberta, Edmonton, Canada. Patients with LBP were recruited voluntarily from the local community by a widely circulated poster advertisement. Inclusion criteria for participation were non-specific LPB of at least 3 months duration resulting in mild to moderate

levels of disability (Oswestry disability index ≤ 60%), pain intensity score between 3 and 8 points (PI-NRS), and age between 18 and 65 years. Participants were excluded if they had contraindications to the use of electrotherapy, neurological problems (central or peripheral), concomitant physiotherapy or chiropractic treatment, fibromyalgia or general systemic disease conditions, or previous experience with electrical pain relieving modalities.

6.2.3. INDEPENDENT VARIABLES (MEASURES)

Therapeutic alliance

The TA between the therapist and the patient was measured by using the working alliance sub-scale of the Pain Rehabilitation Expectations Scale (PRES) completed at the end of the treatment session. The PRES is a self-reported clinical intervention-specific assessment tool developed to measure proxy efficacy, motivation/ expectations, and working alliance for rehabilitation interventions in LBP patients.[44] Previous psychometric results have provided some validity evidence for the factorial structure of the PRES.[44] In addition, high values of internal consistency for each sub-scale (proxy efficacy α 0.93, motivation/expectations α 0.95, and working alliance sub-scale α 0.96) have been reported.[44]

Level of expectations

Patients were asked to rate their expectations of pain relief using the Credibility and Expectancy Questionnaire (CEQ) completed prior to treatment. The CEQ tool has been widely used in clinical trials in diverse areas such as psychology[45, 46] pharmacology[47] physiotherapy[23], and cognitive-behavioral therapy[48, 49] to determine level of expectations. The CEQ comprises 6-items (2 sets) and two factors (i.e. credibility and expectancy). Items 1 to 3 measure credibility, while items 4 to 6 measure expectancy. Respondents were asked to rate items on a scale of 1 to 9, with anchors provided for 1 ("not at all), 5 ("somewhat"), and 9 ("very").[50, 51] The CEQ is considered to be a valid and reliable[51] tool to measure the expectancy construct.

Muscle pain sensitivity

Muscle pain sensitivity was evaluated through the pressure pain threshold (PPT), or the minimum pressure that induces pain or discomfort.[58] PPT measurements have been shown to have good or excellent inter-rater ICC values ranging from 0.74 to 0.90[59] and intra-rater reliability ICC values ranging from 0.75 to 0.99.[60-64] In addition, good values of sensitivity (0.77 to 0.88) and specificity (0.87 to 0.94) for conditions such as myofascial pain and fibromyalgia have been reported.[65, 66] The minimal clinically important change calculated for this outcome has been reported to be ≥ 1.10 Kg/cm^2/s [35, 36]

6.2.4. DEPENDENT VARIABLE (PLACEBO RESPONDER)

In this study, a placebo responder was considered to be a participant with a clinically relevant decrease in his/her LBP intensity score of ≥ 2 points on the 0-10 PI-NRS, as a result of the sham IFC intervention applied in either a limited or an enhanced TA. Patients were evaluated by a blinded outcome assessor and the timing of outcome assessment was similar in both sham groups. The PI-NRS is a self-report measure of pain intensity.[52] The PI-NRS involves the patients rating their pain intensity by selecting a number on a horizontally depicted 11-point scale from 0 (no pain) to 10 (worst possible pain).[53] In patients with chronic LBP, the PI-NRS has been shown to be a reliable and valid measure of pain severity.[54, 55] The minimal clinically important change for LBP has been reported to range from 1.5 to 3.2 points.[56] Other authors have determined a meaningful clinical change of 2 points from baseline pain scores,[41-43, 57] thus this level of change on the PI-NRS score was chosen to indicate a placebo response to sham intervention.[41-43] Baseline pain intensity was also included as a potential determinant for the placebo response.

6.3. ANALYSIS

To examine the determinants of a placebo response, a multiple logistic regression analysis was performed. The outcome for this analysis reflected whether or not the subject was a placebo responder (yes/no). We followed a backward stepwise procedure to determine the most important variables in the model. We started by

including all eight variables (i.e. gender, age, participant's baseline values of pain (PI-NRS), pain duration, therapeutic alliance score (PRES), participant's expectations, participant's baseline muscle pain sensitivity, and participant's level of disability) and we discarded them based on p value. Variables with higher p values (> 0.20) were not further included in the models. As a result of the exploratory screening and selection process, the final model included the following variables of interest: gender, baseline values of pain (PI-NRS), pain duration, therapeutic alliance, and participant's expectations. Based on Peduzzi's et al [67] recommendations for sample size in logistic regression, 58 participants were deemed adequate for five determinants in the final model.

The level of significance was set at $\alpha = 0.05$. Blinded data analysis was performed since each subject and condition was coded by an independent assistant not involved in the trial. The computer program SPSS version 17.0 and STATA version 10 were used for all analyses (SPSS Inc. 233 S. Wacker Drive, Illinois USA, StataCorp LP 4905 Lakeway Drive College Station, Texas 77845 USA).

6.4. RESULTS

6.4.1. PARTICIPANTS

A total of 117 participants with chronic LBP were enrolled in the parent study. From these 117 participants, 58 (i.e. SL= 29, SE= 29) were included in the present study. Their mean age was 30.1 years (SD= 6.1, range = 20 -65 years). As none of the 58 participants withdrew, complete data was available for all of them. As

indicated in Table 1, baseline values for variables used as determinants for the placebo response were not significantly different among groups (p>0.05).

Table 1. Baseline values for the potential placebo determinants

Variables	SL (n=29)	SE (n=29)	Mean differences	P value
Age	30.3 (11.22)	29.8 (10.78)	0.483	1.00
PPT initial	3.7(1.81)	4.5 (2.39)	-0.810	0.74
PI-NRS initial	40.9 (10.96)	41.0 (12.91)	-0.103	1.00
CEQ initial	15.2 (4.50)	15.6 (4.80)	-0.390	1.00
Chronicity (months)	51.1 (38.19	47.2 (87.29)	3.860	0.97
Disability	20.6 (9.54)	21.3 (9.65)	-0.690	1.00

Data are presented as mean and standard deviation. Significant differences P<0.05
SL= sham limited, SE= sham enhanced, PPT= pressure pain thresholds (kg/cm^2/sec), PI-NRS= pain intensity numerical rating scale, CEQ= credibility expectancy questionnaire score, Disability (oswestry questionnaire).

6.4.2. OUTCOMES

Determinants of placebo response

The logistic regression analysis showed that the level of TA (odds ratio 1.22; 95 CI (1.08 to 1.38); p = < 0.01) and pain duration (odds ratio 0.96; 95 CI (0.93 to 0.99); p < 0.01) were the only two factors significantly associated with the placebo response (see Table 2). No other variables were statistically significant in the final model. For the TA an OR of 1.22 indicates that for each point increase in level of the TA on the PRES scale, the likelihood of being a placebo responder increases by a factor of 1.21. As an example, in this study, a significant difference in the PRES scale of 11 points favouring the enhanced group (SL= 30.69; SE 42.45) was found (see Table 3). Therefore, this increase in the TA in 11 points

should be interpreted as 8.14 OR the likelihood of being a placebo responder [68] for the SE group.

Table 2. Results of logistic regression examining associations with placebo response.

Placebo responder	**Odds Ratio**	**[95% C. I.]**	**Std. Error**	**P value**
Gender (female)	0.44	0.15, 1.31	0.24	0.14
Adjusted Odds Ratio	0.20	0.03, 1.06	0.17	0.06
Expectancies level (CEQ)	1.12	0.99, 1.27	0.07	0.06
Adjusted Odds Ratio	1.07	0.90, 1.28	0.09	0.41
Therapeutic alliance (PRES)	1.18	1.07, 1.31	0.05	0.00
Adjusted Odds Ratio	1.22	1.08, 1.38	0.07	0.00
Baseline pain intensity (PI-NRS)	1.03	0.98, 1.08	0.02	0.12
Adjusted Odds Ratio	1.04	0.97, 1.11	0.04	0.32
Pain duration	0.96	0.94, 0.98	0.01	0.00
Adjusted Odds Ratui	0.96	0.93, 0.99	0.01	0.00

Table 3. Mean differences from baseline between the SL and SE groups for pain, muscle pain sensitivity. Therapeutic alliance scores were obtained at the end of the session.

Outcomes	**SL (n=29)**	**SE (n=29)**	**Mean differences**	**P value**
PRES scale	30.69 (5.97)	42.45 (2.66)	-11.759	0.00
PPT ($kg/cm^2/sec$)	0.41 (0.90)	1.75 (1.31)	-1.341	0.00
PI-NRS (mm)	9.70 (6.86)	22.0 (7.13)	-12.29	0.00
CEQ	16.07 (6.75)	18.48 (5.40)	-2.414	0.44

Data are presented as mean and standard deviation. Significant differences P<0.05
SL= sham limited, SE= sham enhanced, PPT= pressure pain thresholds (kg/cm2/sec),
PI-NRS= pain intensity numerical rating scale, CEQ= credibility expectancy questionnaire score

6.5. DISCUSSION

In this study, several potential determinants of the placebo IFC response were evaluated. With the exception of TA and pain duration, no other personal (i.e. gender, age), psychosocial (i.e. expectations), or condition-related factors (i.e. baseline pain scores, disability, muscle pains sensitivity) were found to be associated with the placebo response.

6.5.1. PLACEBO DETERMINANTS

Growing evidence in recent years suggests that therapeutic alliance (TA) plays a pivotal role in clinical outcomes.[69-76] However, its role in the placebo response is not well understood. In this study, a strong association of TA with the placebo analgesia was demonstrated. This study adds to previous research suggesting that the TA is an important determinant of the placebo response.[39] As per the hypothesis, the association of TA with the placebo response observed in this study is in the expected direction.

In this study, both the sham limited (SL) and the sham enhanced (SE) groups received similar IFC placebo interventions. They only differed in the level of interaction between the therapists and participants during the delivery of the placebo intervention. For example, therapists in the SL groups treated the participants with a minimal interpersonal interaction. In contrast, when delivering the treatment in the SE group, therapists used an emphatic and supportive patient-practitioner relationship. As shown by the scores in the PRES scale, [44] results indicate that the TA for the limited group (score 30.69) and enhanced group

(score 42.45) were different (see Table 3). Therapists in the SE group were able to foster a positive interaction with the participants compared with the therapists in the SL group. Based on these values, participants perceived the therapeutic interaction in the SE group as meaningful. Correspondingly, high levels of TA displayed in the SE group had not only a meaningful impact on the clinical outcomes (i.e. pain intensity and pain thresholds) as presented in the parent study but also on the placebo response as shown in this study.

These results are in agreement with a previous trial involving patients with irritable bowel syndrome in which patients were treated with placebo acupuncture in either a warm and empathic interaction or in a neutral interaction. [39] The authors concluded that certain patients' personality traits such as extraversion and openness to experience, as well as the quality of the TA , were associated with the placebo response. Although important differences exist between these two studies regarding the clinical conditions (irritable bowel syndrome versus LBP) and the placebo interventions (acupuncture versus IFC), both studies are similar in the application of scripted and standardized protocols to create the two different therapeutic contexts (i.e. limited interaction versus enhanced interaction). Thus, it is possible that when positive patient-clinician interactions are achieved, despite the different patient populations, TA becomes a consistent determinant of the placebo response.

Due to the association of placebo effect and the affective component of pain, [77] it was expected that the duration of the chronic LBP and the emotional implications thereof, the greater would be the desire for pain relief, a well-known mechanism

of the placebo effect. [8, 9] However, the results of this study showed the opposite direction. Thus, the shorter the duration of pain, the greater was the likelihood of being a placebo responder. We do not have a satisfactory explanation for this finding and we can only speculate that as the average age for participants in this study was 30 years old, we believe that a strong emotional component and the desire of pain relief may not be greatly present in more young LBP subjects population. In addition, the greater the duration of pain, the less likely the patients are to respond to any treatment or placebo. Thus, the pain just becomes intractable and non-responsive to interventions. Finally, it is possible than participants with short pain duration were more receptive to the treatment compared with participants with longer chronicity.

Of interest was the lack of association between participant's expectations and the placebo response found in the present study. Placebo analgesia is a robust psychological and neurophysiological phenomenon that appears to be dependent largely on expectation. This construct has been considered an especially likely predictor of placebo response. [8, 9, 78] However, contrary to the study's hypothesis, the level of expectations was not significantly associated with the response to placebo IFC. It is also possible that differences in the conditions and placebo procedures explored in previous studies would explain this discrepancy. For example, previous studies supporting the predictive role of expectations in the placebo response included conditions such as thoracotomy[6], irritable bowel syndrome [8, 9]and healthy subjects under experimental pain.[26] Correspondingly, placebo manipulations in these studies included placebo intravenous drugs,[6]

placebo rectal drug,[8, 9] and placebo cream.[26] Thus, because of the heterogeneity in patient characteristics mentioned above, associations found in these previous studies might not be transferable to other types of conditions such as LBP. Therefore, it is feasible that musculoskeletal chronic conditions (i.e. LBP) and placebo manipulation through electrophysical agents (i.e. IFC) are not an amenable combination for expectations to be associated with a placebo response. In addition, as shown in the double-blind randomized trial, moderate scores in the CEQ [50, 51] for expectations for both the SL and the SE did not change dramatically after receiving the treatments (SL CEQ 15.2 baseline -CEQ 16.0 after; SE CEQ 16.0 baseline -CEQ 18 after) thus we believe that although participants may have perceived the treatments as genuine, it is unlikely that treatments had instilled highly positive expectations, thus compromising the association effect between expectations and placebo response.

The lack of association between expectations and the placebo response in the present study is in agreement with two recent trials.[27,79] Wasan et al. 2010,[27] explored the effect of expectations on the response to verum and sham acupuncture in chronic LBP. The authors found that expectations interacted significantly with the verum condition but not with the placebo treatment. Similar findings were pointed out in a randomized controlled trial comparing sham acupuncture and sham pill in patients with upper arm pain in which expectations were not associated with the placebo response. [79] Taken together these results suggest more research is needed to better define this construct before its role in placebo response can be definitively determined. In addition, these reports

confirm the complex analysis of placebo determinants. Further, it supports the notion that although some evidence exists regarding personal variables associated with the placebo effect (e.g. female gender)[39], identification of placebo responders is difficult because there does not appear to be a "placebo prone" personality.[80-82]

Baseline pain scores have been considered a predictor for placebo response in chronic musculoskeletal pain such as OA.[19, 83] Both high (> 70% on a 0-100mm VAS) baseline and moderate (35% -70% on a 0-100mm VAS) pain levels have been suggested as placebo determinants in these studies.[19, 83] Some authors support these findings, suggesting that moderate pain scores would be an ideal therapeutic window for placebo analgesia and the dose-response effect of minor analgesics.[83] Although in this study the average baseline pain score was moderate (SL 40.3 mm; SE 41.0), no significant interaction between pain scores and placebo response was found.

6.5.2. LIMITATIONS

Several limitations of this study deserve consideration. First, although the patients in the present study responding to the single application of sham IFC could be labeled as "placebo responders", it is uncertain if these participants are reliable placebo responders.[80] In other words, it is unclear whether or not participants who responded favourably to a single sham IFC application would respond similarly in multiple sham IFC treatments or in more realistic clinical settings. Therefore, future research must focus on understanding the behaviour of participants to

multiple placebo administrations in similar conditions. However, this may be ethically questioned. Similarly, one cannot determine if the placebo responders in this study would respond in the same fashion when receiving a different type of sham intervention. (i.e. consistent placebo responder).[80] Future research must answer these relevant questions. In addition, this is the first study in using the PRES as a tool for TA in rehabilitation for LBP. Although this tool was selected based on its amenability for rehabilitation, its psychometric properties are not fully developed.[44] Finally, given that this study was conducted in LBP and using placebo IFC, it is unclear whether these findings could be extrapolated to another musculoskeletal condition or to a different type of placebo intervention.

6.6. CONCLUSION

Results of this study indicate enhanced TA and shorter pain duration are positively associated with the placebo analgesia response in participants with chronic LBP. This study highlights the power of the TA between therapist and patient in producing placebo effects, and suggests that the quality of this interaction not only is a major determinant for the placebo response but also considerably influences the size of placebo effect in chronic LBP. These findings have implications for future research in physiotherapy helping to characterize placebo responders.

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CHAPTER 7

GENERAL DISCUSSION AND CONCLUSIONS

7.1. DISCUSSION

The prevailing biomedical model and regulatory requirements of clinical researchers encourage study designs demonstrating specificity of the active ingredients of a treatment. [1, 2] In addition, medical training in chronic pain has become increasingly dependent on technique or technical expertise.[3] This may have contributed to a decreased focus on "nonspecific" (i.e. placebo) aspects of treatment. Given the privileged status of specific effects, it is not surprising that the clinical repercussions of the nonspecific treatment effects and the determinants of placebo analgesia in chronic pain are routinely ignored.

Recent consensus panels suggest that conservative interventions for low back pain (LBP) could share common nonspecific mechanisms and that these could influence clinical outcomes. [4-6] Researchers have also outlined that these nonspecific mechanisms, particularly the interaction between patients and clinicians (i.e. therapeutic alliance) could be manipulated in an attempt to achieve substantially better outcomes.

For patients with chronic LBP, this therapeutic alliance has been shown to be predominantly relevant in physiotherapy. [7, 8] However, to date no randomized controlled study has been carried out to assess the significance of the therapeutic alliance for chronic LBP patients in physiotherapy.

Therefore, the main purpose of the present research thesis was to determine the impact of the therapeutic alliance, as a nonspecific aspect of treatment, on clinical outcomes as well as to identify the contributors to the physiotherapy placebo response in patients with non-specific chronic LBP.

This research thesis mainly explored the relevance of the patient–clinician relationship within the area of chronic pain, comparing the effect of a limited therapeutic alliance and enhanced therapeutic alliance on pain intensity (using a numerical rating scale (PI-NRS)) and muscle pain sensitivity (using pressure pain thresholds (PPT)) in both active and sham interferential current treatments (IFC). We also examined the determinants of a favorable response to the contextual factors (i.e. placebo response).

In the research, it was found that clinical meaningful improvements in clinical outcomes were displayed in the groups (active and sham IFC) receiving the enhanced therapeutic alliance compared to the groups in the limited therapeutic alliance (active and sham IFC). In the same way, perceived therapeutic alliance was found associated with a placebo response. Thus, the results of this research thesis provide further evidence that the context in which the treatment is applied is critical for pain outcomes as well as for the pain experience. In addition, the results confirm that the therapist and the patient-therapist interaction is a potent factor in achieving clinically meaningful improvements as well as facilitating the placebo effect.

In the health professions, patients' outcomes can be explained as the results of more than treatment regimens alone.[3, 9] For example, there is evidence from different health disciplines suggesting that a favourable response to treatment depends at least as much on the relationship between the patient and the clinician as it does on the technical aspects and/or the specific effects of an intervention. [3, 10-12] It has been proposed that central to treatment success is a functioning patient-clinician relationship.[5] In addition, the quality of this therapeutic alliance has a stable and predictable effect on outcome and this effect is potentially one of the hallmark ingredients of effective intervention.[13]

In rehabilitation, correlational and retrospective observational studies have shown that higher levels of therapeutic alliance, meaning more positive interactions, are consistently associated with greater improvements in perceived effect of treatment, physical functioning and reductions in pain and disability. [8, 14, 15]

Physical rehabilitation disciplines, including physiotherapy, typically exhibit high levels of patient-clinician interaction. Because of the nature of therapeutic interventions (e.g. touch, care, attention), physiotherapists have an opportunity to build quality relationships with their patients. Since the placebo effect is directly associated with the degree of such interaction, the therapist becomes a major contributor to the placebo response in physiotherapy.[16] In contrast, placebo effects will probably be less effective when the therapeutic alliance between patients and clinicians is limited.

Current work in patient-clinician relationships with relevance to chronic pain has identified two broad components: [17, 18] (1) characteristics of the clinician that

serve to strengthen rapport between the patient and provider, and (2) collaboration and congruence between the patient and clinician in the identification of treatment goals and objectives.

Within the psychotherapy and medical literature, a number of clinician characteristics have been related to a higher quality relationship and better treatment outcomes. [3, 19-21] These characteristics include being perceived by patients as genuine, with good communication skills, empathetic, respectful, and responding to the opinions and perceptions of the patient. Although no studies have examined the specific role of these characteristics in chronic pain settings, it would seem reasonable to hypothesize that clinicians who communicate poorly, who are deemed harder to work with, or who treat in more "unsettled" treatment environments may develop weaker relationships with patients and this in turn, will diminish the probability of beneficial treatment results.[13]

Three essential components that contribute to the therapeutic alliance are: agreement on treatment goals, agreement on interventions, and the development of an affective bond between the patient and therapist.[22] Therefore, an optimal therapeutic alliance is achieved when patient and therapist share beliefs with regard to the goals of the treatment and view the methods used to achieve these as efficacious and relevant. [23]

Mutual understanding and agreement on completing the procedures is critical when performing rehabilitation treatments.[24] In the same way, consistent evidence indicates that better outcomes are achieved when clinician and patient are working together in a collaborative way toward compatible treatment objectives.[25-27] In the

rehabilitation field, negotiations are needed between patients and clinicians to reach mutual agreement to work together in treatment planning, identification of treatment goals and objectives that are being proposed. These interactions involve assurances, dialogue and a high degree of trust. [24] Quite often, the implementation of rehabilitation plans require a high level of commitment and patient adherence that are far more complex that what is required to take medications, for example. This process necessarily needs to be a shared decision making between patients and clinicians. In chronic pain settings, the more patients feel that decision making is shared, the more satisfied they are with treatment which can be translated into better outcomes.[25, 27]

Treatment of chronic pain is often complex. The absence of this shared decision making process or difficulties in engaging in collaborative treatment may add further complexities that can contribute to less effective treatment responsiveness. There is a general view that LBP is a phenomenon of more complexity than has been appreciated in the past.[6] This may explain why the final remarks from recent consensus panels agree that the next set of priorities in LBP research need to include practical trials of early risk profiling and therapeutic alliance skills, understanding the origin of nonspecific effects and expectations to improve outcomes.[4-6] It seems that clinical management of chronic LBP will likely require attention to novel approaches associated with nonspecific treatment effects, to improve treatment responsiveness.

7.2. CONTRIBUTIONS TO PHYSIOTHERAPY

Given the difficulties that are often inherent to the management of chronic pain, it has become relevant to explore all factors that potentially could influence the clinical efficacy of interventions. In this regard, as presented above, recent forums have highlighted the role of the nonspecific effects when treating chronic low back pain.[4-6] In this context, the therapeutic alliance emerges as a concept that needs to be considered if interventions in LBP are to be more effective.

The results of the present thesis emerge as relevant evidence to corroborate this point. This research thesis had a strong clinical emphasis. It was designed and developed to answer clinical questions. It has been suggested that the nonspecific factors, especially the therapeutic alliance, are associated with improved outcomes in chronic pain. [8, 12] However, to date no study had directly confirmed this notion. Since the present research thesis involved the experimental manipulation of the therapeutic alliance, a causal effect can be confirmed.

The results of this research thesis have several implications for contributions to the area of physiotherapy and the management of chronic musculoskeletal conditions. The specific clinical contributions of this project to physiotherapy obtained from each of the areas investigated in this project include the following:

1. First of all, the results provide a base to promote more research in this area. From the information presented in the preliminary chapters, including the literature review and pilot study, it was shown that better

designed and conducted studies are needed to support the evidence of nonspecific effects of treatment in rehabilitation.

2. This research thesis also provides some insight into how the placebo phenomenon operates in healthy subjects under experimentally-induced pain when receiving physiotherapy treatment. Based on the results from the pilot study, mechanically-induced pain is likely not the most appropriate model to elicit a placebo effect. In addition, the modest pain modulator effect shown for the placebo application in the participants from the pilot study may be explained by the absence of strong verbal suggestions of treatment benefit, and the associated expectations, along with the limited therapeutic alliance (TA) used when the treatment was delivered.
3. In the area of physiotherapy, placebo literature is scarce, mainly based on clinical experiences and extrapolated from other disciplines such as psychotherapy and medicine. This research provides the first randomized controlled study addressing the impact of the therapeutic alliance on pain modulation in patients with chronic LBP receiving physiotherapy.
4. The results of this research thesis showed a clear dose-response effect, where the largest beneficial effect occurred in the active IFC group with enhanced therapeutic alliance (TA) and the smallest effect was displayed by the sham IFC in a limited TA. These results suggest that maximizing TA during therapy is accompanied by significant therapeutic benefits. This demonstrated that the additive effect of the two components (specific and

nonspecific) of the therapy can be deliberately maximized to the patient's benefit. These findings call for a more in-depth consideration of contextual factors when delivering therapy. Thus, physiotherapists should consider optimizing the therapeutic clinical context in the management of chronic pain conditions.

5. This research highlights the power of the therapeutic alliance between a clinician and patient in producing placebo effects, and suggests that the quality of this interaction not only is a major determinant for the placebo response but also considerably influences the size of placebo effect in chronic LBP. These findings have implications for future research in physiotherapy helping to characterize placebo responders.

7.3. CLINICAL RECOMMENDATIONS

The results of recent systematic reviews and meta-analyses about common non-pharmacological interventions used by physiotherapists to treat chronic LBP have shown similar and modest short-term benefit, but little long-term benefit. [28, 29] It is plausible that these limited results occurred because contextual factors (e.g. TA) inherent to clinical encounters were not encouraged during the application of interventions in these controlled trials. In clinical settings, it is possible that treatments applied in a neutral or in a 'business-like manner' (i.e. the contextual factors were not enhanced) may translate into less than optimal clinical outcomes.

As discussed earlier, contextual factors are important determinants of a placebo response. The first and foremost aspect of the psychosocial context is the therapeutic alliance between a patient and a clinician.[30] By listening, saying the appropriate things, and physically contacting the patient either during the assessment or treatment, a strong placebo effect may be induced, whereas inappropriate comments can exacerbate the symptoms.[31] A logical step would therefore be to enhance the response to placebos by influencing these factors.

How can clinicians maximize the nonspecific effects of treatment and what specific strategies for improving patient–clinician interaction in the context of pain rehabilitation can be recommended? Very recent studies published in the field of psychotherapy and rehabilitation summarize some key recommendations applicable for most health care settings, but they seem particularly relevant to chronic pain management. [7, 18] A list of several specific clinical actions has been proposed; clinicians who succeed in showing empathy, communicating effectively, providing encouragement, developing trust, agreeing on treatment goals and methods to reach them, responding to the opinions and perceptions of the pain patient, and including the patient in treatment can assume that these behaviors are associated with better treatment outcomes.

In addition, in musculoskeletal conditions, providing positive feedback, answering the patient's questions, and providing clear instructions for home practice are positively correlated with a good working alliance that can impact treatment outcomes. [12] All of these components can even be present in a relatively short

patient encounter, as shown in the present research by just one session of treatment, but they may have lasting consequences in terms of patient outcome.[3] In order to maximize the benefits of physiotherapy, a patient centered approach may be recommended between the physiotherapist and the patient, with enhanced effectiveness of communication regarding specific tasks required to achieve specific treatment goals.[12]

Instead of focusing primarily on the therapeutic power of specific interventions, physiotherapists should consider optimizing the psychosocial context in which the treatment is being delivered for the patients' benefit. This is especially relevant when existing physiotherapy treatments are only partially effective in relieving symptoms for chronic pain conditions such as chronic LBP. [28, 29] All aspects of the therapy (e.g. therapist's words, medical devices) can carry a healing meaning, and therefore must be considered carefully. In an ideal scenario, physiotherapists would combine the power of modern technologies, better therapeutic approaches, and the therapeutic value of the placebo effect, specifically including an enhanced therapeutic alliance. Physiotherapists need to see the context of the clinical encounter as a potential enhancer or even the primary vehicle of therapeutic benefit. [32] In other words, the therapeutic alliance may be considered as another therapeutic agent. Therefore, physiotherapists' awareness of this factor when delivering their interventions could lead to better outcomes.

As Sir William Osler, a Canadian born physician, stated, "The good clinician treats the disease; the great clinician treats the person who has the disease."[33] Physiotherapists must devote their attention to the patient and the patient

encounter to maximize the nonspecific effects of treatment for the patient's benefit.

7.4. FORMALIZED TRAINING IN PATIENT-THERAPIST INTERACTIONS

Specialty training for physiotherapists in the management of musculoskeletal pain (i.e. LBP) has become increasingly technical. Currently, practitioners need to be competent in orthopedic assessment as well as having multiple skills or treatment approaches such as manual therapy, electrotherapy, acupuncture, and therapeutic exercise. Training sessions at conferences and specialty courses tend to focus on learning technical skills. This has more to do with emphasizing the specific effects or being a skilled technician rather that being a compassionate care provider.[3]

In light of the evidence about the impact of the nonspecific effects (i.e. placebo effects) of the treatment, and specifically the effect of the therapeutic alliance on clinical outcomes in rehabilitation,[8, 12] physiotherapy programs and pain specialists could benefit from practice sessions designed to teach interpersonal skills used in patient-physiotherapist interactions.

Effective training methods may include formal courses for physiotherapy students, designed to improve their interpersonal skills based on the principle that effective interactions can be learned. [3] In addition, techniques such as learned scripts, videos, and role-playing with simulated patients [10] ,such as the one included in this present research thesis, could be useful for training students in positively interacting with patients as well as emphasizing the impact of the

therapeutic alliance during clinical encounters on clinical outcomes. Healthcare professionals need to be educated about the characteristics and underlying mechanisms of the nonspecific effects (i.e. placebo effects) so they can optimize placebo components of the therapy.

7.5. FUTURE RESEARCH

This research thesis represents the beginning of an area of research in this field. Future research in this area may provide a useful framework for both understanding, and even empowering the placebo effects and the therapeutic relationship (TA) in physiotherapy. Some directions for future investigations would be:

1. To confirm the beneficial effects of enhanced TA in other musculoskeletal conditions. Given that this research was conducted in chronic LBP and using sham IFC, it is unclear whether these findings could be extrapolated to other musculoskeletal conditions or to a different type of sham intervention. Data from a broader spectrum of musculoskeletal disorders (e.g. chronic neck pain) and different condition states (e.g. acute and chronic) would help to further elucidate the significance of TA in the management of musculoskeletal pain.
2. To determine if the reported benefits of enhanced TA for the patients could be sustained in a longer term. Since the research protocol applied in

the present research aimed to test the immediate effect of the TA, this included just one treatment session. Therefore, it is unclear if the positive effects of TA in clinical outcomes will differ when assessed after a series of treatments or at follow up. Examining this on the basis of protocols including series of treatments and follow-up assessment could be the subject of future research.

3. To evaluate the long term effect of different levels of the TA on pain outcomes, and comparing it against a "no treatment" control group. To avoid the confounding effect of statistical phenomenon such as regression to the mean or the spontaneous temporal variation of pain on the therapeutic effect of the TA, clinical trials need to include an untreated group (i.e. natural history) or untreated baseline condition. [34]
4. To identify unique or overlapping contributions of different components of the TA. Although various components (i.e. active listening, communication, empathy, encouragement) of the patient–clinician relationship were included in this research, it is difficult to determine the extent to which they overlap or which, if any, is of exceptional importance. While it may be possible to identify unique and overlapping contributions statistically, it also may be necessary to investigate the individual contributions of these specific aspects of the patient-clinician relationship in future research, specifically via randomization and control.
5. To study the effect of the TA on objective outcomes in chronic musculoskeletal pain. LBP is a condition with many subjective outcomes

such as pain and functional ability. Correspondingly, this research measured the effect of TA on subjective outcomes (i.e. PI-NRS, PPT). The effect of placebo on subjective outcomes is well documented. [35] However, less is known about its impact on objective outcomes in chronic LPB. Therefore, future research should be focused on the analysis of placebo mechanisms in objective outcomes such as the modification of pain relieving peptides or changes in cerebral activity (i.e. neuroimaging) in areas linked with pain processing and pain modulation in patients suffering from chronic musculoskeletal pain. In addition, experimental pain models may be valuable as a method to quantify the effect of placebo in subjects with chronic pain.[36]

6. To further examine the role of different determinants for the placebo response. Patient characteristics such as level of education or ethnicity may have a differential level of association with the placebo response. In addition, therapeutic contextual factors including therapeutic devices or different therapeutic rituals, may have a different level of association with the placebo response and this requires attention in future research.
7. To understand the behaviour of participants in response to multiple placebo administrations. Patients in the present research who responded to a single application of sham IFC were labeled as “placebo responders.” It is uncertain if these participants are reliable placebo responders. Will these participants who responded favourably to a single sham IFC application respond similarly to multiple sham IFC treatments? Similarly, would the

placebo responders in this research respond in the same fashion when receiving a different type of sham intervention (i.e. are they consistent placebo responders)? Future research must answer these relevant questions.

7.6. CONCLUSIONS

The results of this research show that pain is context dependent, modified by contextual factors such as the therapeutic relationship between the patient and clinician. This research thesis represents a unique contribution in determining the clinical impact of nonspecific effects, specifically the therapeutic alliance, on pain modulation in patients with chronic LBP receiving IFC. An enhanced therapeutic alliance while delivering the intervention was associated with clinically relevant changes in pain reduction and decrease of muscle pain sensitivity. This research demonstrated that placebo effects can have meaningful therapeutic effects.

What is clear is that placebo mechanisms can and should be enhanced to maximize the effect of currently available therapeutic agents. Knowledge concerning determinants and mechanisms of placebo effects within active therapies could serve to enhance this component through ethical use of suggestions and optimal clinician-patient interaction. Therefore, by promoting nonspecific effects into therapeutic strategies, treatment responsiveness could be improved.

The therapeutic alliance between patient and clinician appears to be a powerful influence, and physiotherapists need to maximize that power to reduce the suffering of individuals with pain. Efforts to enhance patient–clinician communication as well as to systematically examine nonspecific treatment factors are likely to promote effective management of chronic pain.

Although further research is warranted, these results clearly have important implications, namely that factors other than the specific treatment may have a large role in achieving positive clinical outcomes, and exploring them is central to advancing physiotherapy practice.

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8. APPENDICES

8.1. ADVERTISING TO RECRUIT SUBJECTS

UNIVERSITY OF ALBERTA

Faculty of Rehabilitation Medicine
Department of Physical Therapy

The Pain Relieving Effect of Interferential Stimulation Therapy in Chronic Low Back Pain

-

Are you having pain in your back, are you between 18-60 years old?

If so, we invite you to participate in our study of the pain-relieving effect of electrotherapy. During the electrotherapy treatment, you may feel a comfortable sensation in your back.

You will need to attend 1 session of 60 min.

If you wish participate or find out more information call (780) 492-4824, (780) 717-7323, or send an email to Jorge Fuentes jorgef@ualberta.ca

8.2. CONSENT FORM

Title of Project: Therapeutic Contextual Factors in Physiotherapy
Principal Investigators: Douglas Gross, Ph.D., David. Magee Ph. D. , Jorge Fuentes MSc
Phone: 780- 492-4824 or email jorgef@ualberta.ca

	YES	NO
Do you understand that you have been asked to be in a research study?		
Have you read and received a copy of the attached Information Sheet?		
Do you understand the benefits and risks involved in taking part in this research study ?		
Have you had an opportunity to ask questions and discuss this study?		
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without consequence?		
Has the issue of confidentiality been explained to you?		
Do you understand that the researchers will not have access to any health records?		
Do you consent to the use of your image in pictures or videos when presentation about this research are made?		

This study was explained to me by:
_____

I agree to take part in this study: YES ☐ NO ☐

Signature: _____

Printed Name: _____

Date:_____

Signature of Witness

_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date_____

8.3. CREDIBILITY AND EXPECTANCY QUESTIONNAIRE

(Modified from Borkovec & Nau 1972, Devilly & Borkovek 2000)

1. At this point, how logical does the therapy offered to you seem?

1 2 3 4 5 6 7 8 9

not at all logical somewhat logical very logical

2. At this point, how successfully do you think this treatment will be in reducing your limitations due to back pain?

1 2 3 4 5 6 7 8 9

not at all useful somewhat useful very useful

3. How confident would be in recommending this treatment to a friend who experiences low back pain

1 2 3 4 5 6 7 8 9

not at all confident somewhat confident very confident

4. By the end of the therapy period, how much improvement in your limitation due to back pain do you think will occur?

0% 10% 20 % 30% 40% 50% 60% 70% 80% 90% 100%

For this set, close your eyes for a few moments, and try to identify what you really *feel* about the therapy and its likely success. Then answer the following questions

5. At this point, how much do you really feel that the therapy will help to reduce your limitations due to back pain?

1 2 3 4 5 6 7 8 9

not at all somewhat very much

6. By the end of the therapy period, how much improvement in your limitations due to back pain do you really feel will occur?

0% 10% 20 % 30% 40% 50% 60% 70% 80% 90% 100%

8.4. WORKING ALLIANCE SUBSCALE OF THE PAIN REHABILITATION EXPECTATIONS SCALE (PRES)

Below each statement inside there is a four-point scale: 1 (strongly disagree), 2 (disagree), 3 (agree), and 4 (strongly agree). Please circle the number you consider appropriate

My therapist is positive and gives me encouragement			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist listens to my concerns and issues			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist is optimistic			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist listens to me			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist informed me of what to expect from the treatment (including possible side effects)			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist does a good job of explaining my treatment to me			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist takes my concerns seriously			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist is responsive to my needs			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist is friendly and warm			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist is objective in trying to understand my problems			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree
My therapist is good at communicating with me			
1	2	3	4
Strongly disagree	Disagree	Agree	Strongly agree

8.5. OSWESTRY DISABILITY INDEX VERSION 2.0

Could you please complete this questionnaire. It is designed to give us information as to how your back pain has affected your ability to manage in every day life. Please answer every section. Mark one box only in each section that most closely describes you today

Section 1. Pain intensity

---- I have no pain at the moment
---- The pain is very mild
---- The pain is moderate
---- The pain is fairly severe
---- The pain is very severe
---- The pain is the worst imaginable

Section 2. Personal care (e.g. dressing)

---- I can look after myself normally without causing extra pain
---- I can look after myself normally but is very painful
---- It is painful to look after myself and I am slow and careful
---- I need some help but manage most of my personal care
---- I need help every day in most aspects of self- care
---- I do not get dressed, wash with difficulty and stay in bed

Section 3. Lifting

---- I can lift heavy weights without causing extra pain
---- I can lift heavy weights but gives me extra pain
---- Pain prevents me from lifting heavy weights off the floor
---- Pain prevents me from lifting heavy weights off the floor but I manage light to medium weights from a table
---- I can lift only very light weights
---- I cannot lift or carry anything at all

Section 4. Walking

---- Pain does not prevent me walking any distance
---- Pain prevents me walking more than 2 kilometers
---- Pain prevents me walking more than 1 kilometer
---- Pain prevents me walking more than 500 meters
---- I can only walk using a stick or crutches
---- I am in the bed most of time, I have to crawl to the toilet

Section 5. **Sitt**ing

---- I can sit in any chair as long as I like
---- I can sit in my favorite chair as long as I like
---- Pain prevents me from sitting for more than one hour
---- Pain prevents me from sitting for more than 1/2 an hour
---- Pain prevents me from sitting for more than 10 minutes
---- Pain prevents me from sitting at all

Section 6. Standing

---- I can stand as long as I want without extra pain
---- I can stand as long as I want but it gives me extra pain
---- Pain prevents me from standing more than one hour
---- Pain prevents me from standing more than 1/2 hour
---- Pain prevents me from standing more than 10 min
---- Pain prevents me from standing at all

Section 7. Sleeping

---- My sleep is never disturbed by pain
---- My sleep is occasionally disturbed by pain
---- Because of pain I have less than 6 hours of sleep
---- Because of pain I have less than 4 hours of sleep
---- Because of pain I have less than 2 hours of sleep
---- Pain prevents me from sleeping at all

Section 8. Sex life (if applicable)

---- My sex life is normal and causes no extra pain
---- My sex life is normal but causes some extra pain
---- My sex life is nearly normal but is very painful
---- My sex life is severely restricted by pain
---- My sex life is nearly absent because of pain
---- Pain prevents any sex life at all

Section 9. Social life

---- My social life is normal and causes no extra pain
---- My social life is normal but increases pain
---- Pain has no significant effect on my social life apart from my more energetic interests (e.g. sports)
---- Pain has restricted my social life
---- Pain has restricted my social life to my home
---- I have no social life because of pain

Section 10. Travelling

---- I can travel anywhere without pain
---- I can travel anywhere but it gives extra pain
---- Pain is bad but I manage journeys over two hours
---- Pain restricts me to journeys of less than 1 hour
---- Pain restricts me to short necessary under 30 minutes
---- Pain prevents me from travelling except to receive treatment

8.6. DATA COLLECTION SHEET

Subject data
Code
Gender
Age
Height/ Weight
Educational level/years

PI-NRS	**PPT**	1st measurement	2nd measurement	Mean
Before:	**M1 (-10 min)**			
	M2 (0)			
	M3 (15 min)			
After:	**M4 (30 min)**			

Date:

Comments:

8.7. INTERFERENTIAL THERAPY EQUIPMENT SPECIFICATIONS
(Metron Vector surge 5)

Metron **Vectorsurge 5**

1. SPECIFICATIONS

MAINS POWER SUPPLY REQUIREMENTS:

Voltage	90 - 264 Volts AC
Frequency	50/60 Hz
Power	75 VA Nominal

FUSES:

Primary External	2 of 1 A 5x20 mm Delay
Secondary	1 of 4 A 5x20 mm Delay

MAINS TRANSFORMER:

Integrated switchmode power supply complying with international standard IEC 601-1: 1988 (EN 60601-1) and all subsequent amendments.

Secondary voltages	48 Volts @ 1.7A

OUTPUT SPECIFICATION - INTERFERENTIAL:

Maximum current in each patient circuit	80 mA
Indicator resolution	1 Segment = 4 mA
Indicator accuracy	+/- 10% for currents greater than 10 mA
Maximum voltage in each patient circuit	160 V peak-to-peak
Current Surge Programmes	Disabled or Enabled
Enabled	Rise 0 - 20 seconds On 0 - 40 seconds Fall 0 - 20 seconds Off 0 - 40 seconds
Waveform Beat Frequencies	
Preset Ranges	0 - 15 Hz 0 - 150 Hz 80 - 150 Hz
Adjustable Range	0 - 300 Hz
Current Waveform Type	Modulated Rectangular, 50% Duty Cycle
Waveform Pulse Frequencies	2.5, 4 or 10 kHz
Frequency accuracy	Better than +/- 1%
Waveform Pulse Widths	50, 125 or 200 µs
Current Delivery Modes	2 Pole (Amplitude Modulated) or 4 Pole (Phase Modulated)

8.8. SAFETY STANDARD LETTER

REPORT OF LEAKAGE CURRENT FOR PT PhD STUDENT, JORGE FUENTES ON JUNE MAY 20, 2010 BY AL FLEMING

THE HOSPITAL STANDARD FOR LEAKAGE CURRENT IS 500 MICRO AMPS.

LEAKAGE CURRENT IN MICROAMPS

DESCRIPTION OF EQUIPMENT	U of A#	HOT	NEUTRAL
METRON Vectorsurge 5	508342	0	80

Note: The readings of the leakage current were taking with a BK Precision Model 1655 AC Power Supply and leakage Tester U. of A. # 162679. These devices were well under the 500 micro amp hospital standards.

Al Fleming

8.9. TECHNICAL SPECIFICATIONS AND CALIBRATION FOR THE ALGOMETER

Technical specifications

CONSTRUCTION
- Large 2 1/4" dial. Dual Graduations
- Plastic housing, stainless steel plunger and plastic crystal.

OPERATION
- Compression with 1 cm^2 (7/16") rubber tip.
- Push button maximum reading hold.
- Tension hook for accuracy check with weights.

ACCESSORIES
- Rubber tip, 1 cm^2 (7/16"), 2" long hook, carrying case and manual.
- Optional pressure pad: 3" x 1 1/4".

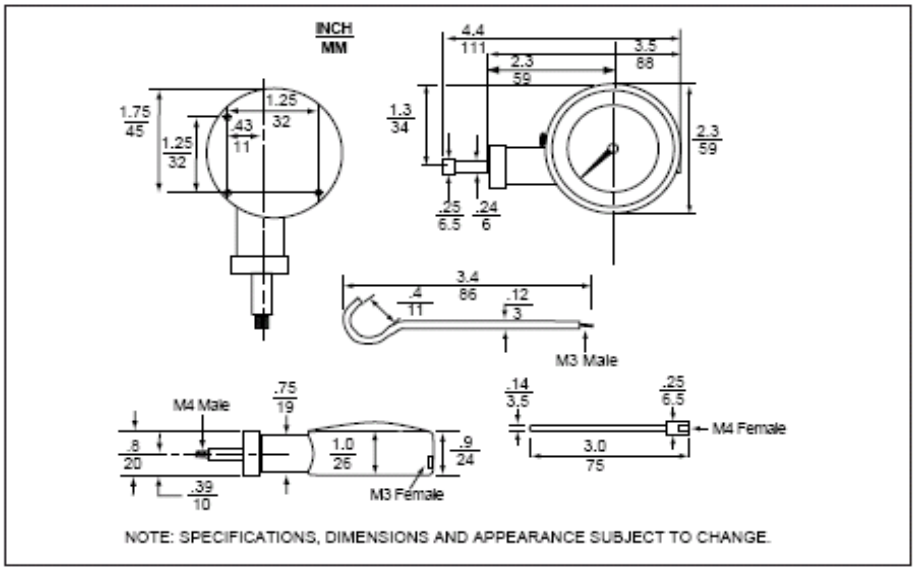
ACCURACY
- ± 2 Grad. (thru 2500 gf), ±1 Grad. (Over 2500 gf).

WEIGHT & DIMENSIONS
- Net weight: 10 oz / 284 g.
- Overall length: 4 1/2" / 115 mm.

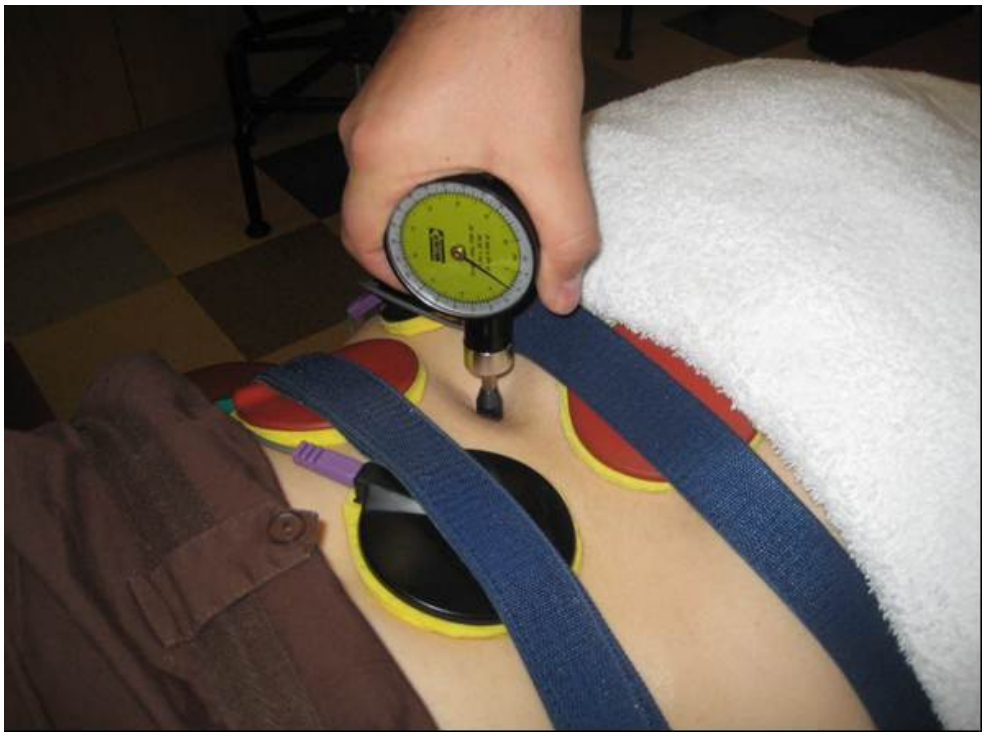
Calibration

- The device is presented with a calibration certified.

- Is calibrated with certified test weights. Periodical testing of the accuracy should be performed with test weights. The weights should be suspended on the securely mounted gage at ¼, ½, ¾ and full capacity.



8.10. EXPERIMENTAL SET-UP



Four carbon rubber electrodes placed over the lumbar area. Mechanical algometer applied perpendicularly over the right erector spinae muscle, 4 cm to the right of the spinous process of L4

8.11. INFORMATION LETTER TO SUBJECTS

UNIVERSITY OF ALBERTA

Title of the research project:

Therapeutic Contextual Factors in Physiotherapy

Researchers:

Douglas P. Gross PhD, David J. Magee, PhD, Jorge Fuentes, PT MSc

Department of Physical Therapy, 2-50 Corbett Hall (Phone 780-492-2690 or 780-492-4824)

What is the study about?

Interferential current is used by physical therapists to treat pain. The purpose of this study is to evaluate whether the application of interferential current produces pain relief in people with low back pain.

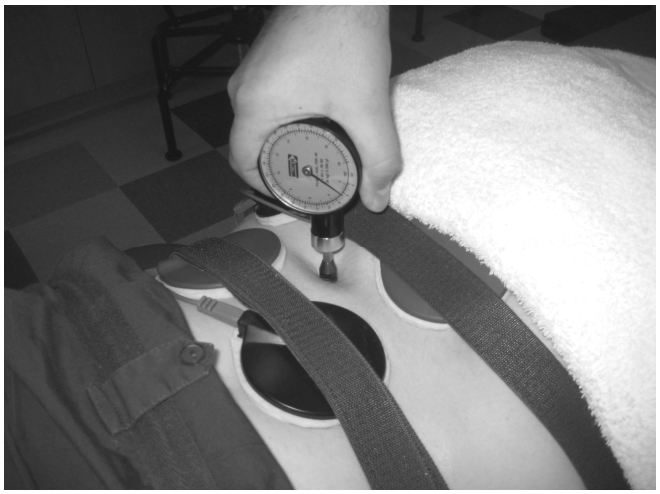
What will you be asked to do?

Initially you will be asked questions to make sure you meet the criteria to be included in the study. If you qualify and agree to participate, you will be asked to come to our laboratory for one visit of 45-minutes. During the session you will receive one treatment of interferential current. Interferential is a treatment

commonly used by physical therapists. During the session, you will lie facing down with your arms relaxed alongside your body. During the treatment, four therapeutic electrodes will be placed on your lower back area. The treatment will be applied for 30 minutes. In order to evaluate if you receive the same treatment that everyone else does, the session will be videotaped.

Pain threshold in your low back will be measured during the treatment session. It will be measured as the amount of pressure needed to cause the first sensation of pain. We will measure pain threshold with a device called an algometer. At the beginning of the session we will demonstrate how this device works. During the procedure you will be asked to say "stop" as soon as you feel a clear sensation of pain when the device is applied. At this point, the device will be removed. Your pain threshold will be assessed four times: 1) 10 minutes before starting treatment; 2) immediately before initiating the treatment; 3) during treatment application; and 4) immediately after finishing.

Experimental set-up:



Your height and weight will also be measured. Before treatment, you will be asked to complete some questionnaires about your level of disability and intensity of your pain. We will also ask some questions about whether you think the treatment will be successful at controlling your pain. After receiving the treatment, you will be asked to complete a questionnaire to assess the quality of the therapeutic relationship. Also, you will be asked to answer about whether you think the treatment was successful at controlling your pain. Finally, the intensity of your pain will be asked again.

What are the benefits?

The benefit of participating in this study is that you can help us to evaluate the effects of interferential current therapy. You may experience short-term pain relief from the treatment. There are no other personal benefits for you as a participant in this study.

Are there any risks?

Application of the algometer may result in slight bruising if applied too strongly. Application of interferential may result in skin irritation if applied incorrectly. However, the chance of this occurring is very small since an experienced physiotherapist is applying the algometer and treatment.

Privacy/confidentiality

All data will be kept private, except where codes of ethics or the law requires. The data you give will be kept in a safe, secure area for at least 5 years after the study is completed. Your name or any other identifying data will not be attached to the data you generate. Your name will never be used in any presentation or publications related to study results. The video of your treatment will be reviewed by two members of our research team unless you chose to allow us to use it in presentations. After that, the videos will be deleted. The data gathered for this study may be looked at again in the future to help us answer other study questions. If so, the Health Research Ethics Board will first review the study to ensure that the data are used ethically.

Freedom to withdraw

Your participation is voluntary. You do not have to take part. If, at any time, you decide to withdraw you are completely free to do so without consequences.

Who should I contact if I have concerns or questions?

If you have any questions or concerns regarding your rights as a research subject, please contact Dr. Joanne Volden, Associate Dean of Research in the Faculty of Rehabilitation Medicine (Phone 780-492-9674).

If you have any questions regarding study procedures you can contact:

Dr. Doug Gross, Phone 780-492-2690, Email dgross@ualberta.ca

Jorge Fuentes, PT MSc , Phone 780-492-4824, Email jorgef@ualberta.ca

8.12. SAMPLE SIZE CONSIDERATIONS

Sample size calculations for a three-group MANOVA

Study	Mean before VAS (SD)	Mean after VAS (SD)	difference
Zambito et al. 2007			
IFC	8.7 (1.1)	4.9 (1.1)	3.8
Sham	8.6 (1.0)	7.0 (1.0)	1.6
Zambito et al. 2006			
IFC	8.2 (1.1)	5.0 (1.0	3.2
Sham	8.1 (1.0)	6.9 (1.6)	1.1

DATA ENTRY							RAW DIFFERENCE					STANDARDISED EFFECT SIZE					
Outcome measure	Treatment group			Control group			pooled standard deviation	p-value for difference in SDs	Mean Difference	p-value for mean diff (2-tailed T-test)	Confidence Interval for Difference	Effect Size	Bias corrected (Hedges)	Standard Error of E.S. estimate	Confidence Interval for Effect Size		Effect Size based on control gp SD
	mean	n	SD	mean	n	SD					lower				lower	upper	
Zambito et al., 2007	3.8	35	1.10	1.6	35	1.00	1.05	0.29	2.20	0.00	1.70	2.09	**2.07**	0.30	1.49	2.65	2.20
Zambito et al., 2006	3.11	35	1.00	1.13	24	1.60	1.28	0.01	1.98	0.00	1.30	1.55	**1.53**	0.30	0.94	2.12	1.24
													%confi 95 p: 0.05 Z-value: 1.96				

Effect size calculations

EFFECT SIZE CALCULATED:

Zambito et al. 2007: 2.09

Zambito et al. 2006: 1.55

Mean effect size (1.82) large effect

Estimated sample size for a four- group MANOVA repeated measures with two outcomes [152] (i.e. PPT, VAS), to detect a change in 30 mm in VAS (Power 0.80, $\alpha = 0.05$, d= 1, 20% attrition) is as follows:

29 per group: (29 x 4 groups) = 116 subjects

Total = 116 subjects

Sample size for the regression analysis will be based on Peduzzi et al. (1996) recommendations: 10 patients X 3 variables (e.g. expectancy level, therapeutic alliance, and disability) = 30 patients.

Therefore, a sample size of 116 individuals will be considered for both the MANOVA and the logistic regression analysis

8.13. THERAPIST SCRIPT FOR THE ACTIVE IFC PLUS LIMITED THERAPEUTIC ALLIANCE GROUP

INTRODUCTION

Good morning/afternoon, my name is XX XX. I will be your clinician today.

…" The treatment that I am going to apply today has been widely used to treat chronic musculoskeletal conditions. For this reason, it is considered a standard electrotherapy therapeutic approach to treat chronic low back pain. …

" The clinical experience I have had with this treatment is promising on other patients. Very often most patients felt better with treatment". "You will receive the treatment for 30 minutes."

TREATMENT

… "During the treatment you will feel a "pins and needles-like sensation" on your back, but no pain or muscle twitches will be present during the application of the treatment" "This intervention is considered a safe modality, and there are no known risks related to the application of this treatment."

… "After completing the set up for the treatment I will leave the room and will remain outside in case you require some attention during the treatment." "Since this is a scientific study, I am not allowed to converse with you during the treatment"

… "I will return to the room at 15 and 30 minutes into the treatment, to be present when the tester arrives to proceed with the assessment of your pressure pain thresholds."

8.14. THERAPIST SCRIPT FOR THE SHAM IFC PLUS LIMITED THERAPEUTIC ALLIANCE GROUP

INTRODUCTION

Good morning/afternoon, my name is XX XX . I will be your clinician today.

TREATMENT

…"Today I am going to apply a new type of therapy called therapeutic sub-threshold current. "This type of treatment has been successfully proven in research studies".

…"Since the level of stimulation is sub-threshold, you might not be able to feel the current" "This intervention is considered to be safe, and there are no known risks related to this treatment." "We want to learn whether this new type of stimulation works by comparing it to a standard treatment." "You will receive the treatment for 30 minutes."

……" The clinical experience I have had with this new treatment is promising on other patients. Very often most patients felt better with treatment".

… "After putting the electrodes on your back, I will leave the room and will remain outside in case you require some attention during the treatment." "Since this is a scientific study, I am not allowed to talk with you during the treatment"

… "I will return to the room in 15 and 30 minutes, and will be here when the tester arrives to test your pressure pain thresholds."

8.15. THERAPIST SCRIPT FOR THE ACTIVE IFC PLUS ENHANCED THERAPEUTIC ALLIANCE GROUP

INTRODUCTION

Good morning/afternoon, my name is XX XX. I will be your clinician today.

First of all I have a few questions to help me understand your pain better. What is the cause of your low back pain? Do you know about what factors can cause low back pain and make it worse? Do these things affect your pain?

I am also interested in your own personal symptoms. Is your pain constant? Can you tell me what type of activities increase your pain? What types of activities reduce your pain?

How low back pain has changed your lifestyle? For example, do you feel that your low back pain is affecting your ability to walk? Sleep? Is pain affecting your social life?

…"Your CLBP must be difficult for you"

TREATMENT

…"For the treatment today I am going to apply a new treatment. You will receive the treatment for 30 minutes; this treatment has been successfully proven in research studies".

…"The treatment you are going to receive can be a very highly effective pain reliever...."The clinical experience I have had with this new treatment on other patients is promising. Very often, most patients felt better after treatment. "

…“During the treatment you will feel a “pins and needles-like sensation” on your back, no pain or muscle twitches will be present during this treatment.” “This treatment is considered safe, and there are no known risks related to this treatment.”

…” I will stay in the room during the whole procedure in case you need help or if you have questions about the treatment. Also, I will be here when the tester arrives to test your pressure pain threshold.

END OF TREATMENT

“You did it very well today”…”You will be fine”… “I do understand that at times, chronic pain can be something that is beyond your control”… “Whatever happens, try to be patient with yourself and look forward to good things that are ahead for you”.

8.16. THERAPIST SCRIPT FOR THE SHAM IFC PLUS ENHANCED THERAPEUTIC ALLIANCE GROUP

INTRODUCTION

Good morning/afternoon, my name is XX XX, I will be your clinician today.

First of all I have a few questions to help me understand your pain better. What is the cause of your low back pain? Do you know about what factors can cause low back pain and make it worse? Do these things affect your pain?

I am also interested in your own personal symptoms. Is your pain constant? Can you tell me what type of activities increase your pain? What types of activities reduce your pain?

How low back pain has changed your lifestyle? For example, do you feel that your low back pain is affecting your ability to walk? Sleep? Is pain affecting your social life?

…"Your CLBP must be difficult for you"

TREATMENT

… For the treatment today I am going to apply a new type of therapy called therapeutic sub-threshold current." "This type of stimulation has been successfully proven in research studies".

…Since the level of stimulation is sub-threshold, you might not be able to feel it beneath the electrodes" "This treatment is considered a safe modality, and there are no known risks related to the application of this treatment." "We want to clinically confirm the efficacy of this new type of stimulation contrasting it against a standard stimulation." "You will receive the treatment for 30 minutes."

…“The treatment you are going to receive can be a very highly effective pain reliever” “The clinical experience I have had with this new treatment is promising on other patients. Very often most patients felt better with treatment”.

…” I will stay in the room during the whole procedure in case you need help or if you have questions about the treatment. Also, I will be here when the tester arrives to test your pressure pain threshold.

END OF TREATMENT

…”You did it very well today…You will be fine”… “I do understand that at times, chronic pain can be something that is beyond your control.”… “Whatever happens, try to be patient and look forward to good things that are ahead for you”.

8.17. EVALUATION FORM FOR THE PROTOCOL ADHERENCE

ACTIVE IFC PLUS LIMITED THERAPEUTIC ENCOUNTER GROUP

INTRODUCTION

1. Did the clinician introduce her/himself?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

2. Did the clinician explain about the type of the treatment she/he is going to apply (e.g. standard treatment)

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

3. Did the clinician mention about her/his previous positive professional experience with the treatment? (e.g. I have had with this treatment is promising with other patients)

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

4. Did the clinician mention that she/he will return to the room and that she/he will be there when the tester arrives to test pain thresholds?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

TREATMENT

5. Did the clinician explain the sensation the patient is going to feel during the treatment?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

6. Did the clinician state that the treatment is safe?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

7. Did the clinician mention that she/he will remain outside the room during the treatment?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

8. Did the clinician declare she/he is not allowed to talk with the patient during the treatment?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

ACTIVE IFC PLUS ENHANCED THERAPEUTIC ENCOUNTER GROUP

INTRODUCTION

1. Did the clinician introduce her/himself?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

2. Did the clinician question patient about causes of low back pain?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

3. Did the clinician question patient about symptoms of low back pain?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

4. Did the clinician question patient about lifestyle and low back pain?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

5. Did the clinician include behaviors such as empathy, active listening (e.g your CLBP must be difficult for you)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

TREATMENT

6. Did the clinician explain about the type of the treatment she/he is going to apply (e.g. new treatment)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

7. Did the clinician include verbal suggestions regarding treatment effectiveness (e.g. the treatment can be a very highly effective pain reliever)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

8. Did the clinician mention about her/his previous positive professional experience with the treatment (e.g. I have had many positive experiences treating painful conditions with this type of intervention)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

9. Did the clinician explain the sensation the patient is going to feel during the treatment?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

10. Did the clinician state that the treatment is safe?

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

11. Did the clinician mention that she/he will stay in the room during the treatment?

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

12. Did the clinician include behaviors such as empathy, active listening during the treatment?

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

END OF TREATMENT

13. Did the clinician include few words of encouragement at the end of the therapy? (e.g. you did it very well today…You will be fine)

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

SHAM IFC PLUS LIMITED THERAPEUTIC ENCOUNTER GROUP

INTRODUCTION

1. Did the clinician introduce her/himself?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

TREATMENT

2. Did the clinician explain about the type of the treatment she/he is going to apply (e.g. new therapy –sub threshold current)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

3. Did the clinician explain the sensation the patient is going to feel during the treatment (e.g. since the level of stimulation is sub-threshold, you might not be able to feel the current)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

4. Did the clinician mention about her/his previous positive professional experience with the treatment (e.g. I have had with this new treatment is promising on other patients)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

5. Did the clinician state that the treatment is safe?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

6. Did the clinician mention that she/he will remain outside the room during the treatment?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

7. Did the clinician declare she/he is not allowed to talk with the patient during the treatment?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

8. Did the clinician mention that she/he will return to the room and that she/he will be there when the tester arrives to test pain thresholds?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

SHAM IFC PLUS ENHANCED THERAPEUTIC ENCOUNTER GROUP

INTRODUCTION

1. Did the clinician introduce her/himself?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

2. Did the clinician question patient about low back pain symptoms?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

3. Did the clinician question patient about causes of low back pain?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

4. Did the clinician question patient about lifestyle and low back pain?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

5. Did the clinician include behaviors such as empathy, active listening (e.g your CLBP must be difficult for you)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

TREATMENT

6. Did the clinician explain about the type of the treatment she/he is going to apply (e.g. new treatment/sub-threshold current)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

7. Did the clinician include verbal suggestions regarding treatment effectiveness (e.g. the treatment can be a very highly effective pain reliever)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

8. Did the clinician mention about her/his previous positive professional experience with the treatment (e.g. I have had many positive experiences treating painful conditions with this type of intervention)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

9. Did the clinician explain the sensation the patient is going to feel during the treatment (e.g. since the level of stimulation is sub-threshold, you might not be able to feel the current)?

   Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

10. Did the clinician state that the treatment is safe?

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

11. Did the clinician mention that she/he will stay in the room during the treatment?

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

12. Did the clinician include behaviors such as empathy, active listening during the treatment?

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***

END OF TREATMENT

13. Did the clinician include few words of encouragement at the end of the therapy? (e.g. you did it very well today…You will be fine)

    Strongly agree *1 2 3 4 5 6 7 8 9 10* ***strongly disagree***