Marcus Yu Bin Pai

Efeito analgésico prolongado do *dry needling* em dor de ombro: estudo randomizado, duplo-cego, sham controlado

Tese apresentada à Faculdade de Medicina
da Universidade de São Paulo para
obtenção do título de Doutor em Ciências

Programa de Neurologia
Orientador: Prof. Dr. Daniel Ciampi de Andrade

São Paulo
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Dry needling has lasting analgesic effect in shoulder pain: a double-blind, sham-controlled trial

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DEDICATION

A special thanks to my children Pedro and Ana Julia.

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ABBREVIATIONS AND SYMBOLS

ºC: Celsius temperature

5-HT: serotonin

ANOVA: Analysis of Variance

ATP: adenosine triphosphate

BK: bradykinin

BPI: Brief Pain Inventory scale

CGRP: calcitonin gene-related peptide

CI: confidence interval

D0: one week before needling,

D7: day of needling

D14: one-week post-needling follow-up:

DN4: douleur neuropathique 4

ESWT: extracorporeal shockwave therapy

H+: hydrogen ion

HADS: Hospital Anxiety and Depression scale

IL-1β: interleukin 1 beta

K+: potassium ion

MPS: myofascial pain syndrome

MSK: musculoskeletal

MQS: Medication quantitative scale

MTrP: myofascial trigger point

MTrP-DN: myofascial trigger point dry needling

NA: noradrenaline

NRS: Numeric Rating Scale

NSAID: nonsteroidal anti-inflammatory drug

QST: Quantitative sensory testing

SDM: Síndrome Dolorosa Miofascial

SF-MPQ: Short-Form McGill Pain Questionnaire

SP: substance P

USP: University of São Paulo

TNF-α: tumor necrosis factor alpha

VAS: Visual Analogue Scale

UNITS

cc: cubic centimeter

cm^2: square centimeter

g: grams

FIGURES

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RESUMO

Pai, Marcus YB. ***Efeito analgésico prolongado do dry needling em dor de ombro: estudo randomizado, duplo-cego, sham controlado*** **[tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2021.**

INTRODUÇÃO: A síndrome dolorosa miofascial (SDM) afeta a maioria dos pacientes com dor crônica no ombro. Agulhamento seco (AS) é uma opção de tratamento comum para MPS, mas seu padrão temporal e efeitos sensoriais permanecem desconhecidos. Avaliamos em um estudo duplo-cego e controlado por sham o padrão de eficácia analgésica e alterações sensoriais locais de uma única sessão de AS para SDM em pacientes com dor crônica no ombro. Pacientes com dor crônica no ombro foram randomizados em grupos ativos (n = 20) ou sham (n = 21). Uma única sessão de AS foi realizada por um pesquisador cego para a atribuição do grupo e os resultados da dor. A intensidade da dor foi avaliada pelo escore numérico (EVN) e os limiares sensoriais foram avaliados com um protocolo de teste sensorial quantitativo (TSQ), incluindo a área de alterações sensitivas táteis sete dias antes do agulhamento, logo antes e sete dias após a intervenção. RESULTADOS: O AS levou a uma redução significativa da intensidade da dor maior (de 6,30 ± 2,05 para 2,40 ± 2,45 no grupo ativo e de 6,04 ± 1,32 para 5,14 ± 1,49 no grupo sham; p = 0,02). Os escores de redução da dor foram significativamente diferentes no segundo dia após o agulhamento e persistiram até o sétimo dia, e foram acompanhados por melhora em outras dimensões da dor e por uma diminuição na área de hiperalgesia mecânica apenas no grupo AS ativo (p <0,05) CONCLUSÃO: O agulhamento seco do ponto gatilho ativo resultou em maior efeito analgésico em comparação com o sham, e diminuiu a área de hiperalgesia mecânica local. Esses achados têm implicações clínicas práticas e podem fornecer percepções mecanicistas sobre a fisiopatologia da SDM.

Descritores: Síndromes da Dor miofascial; Dor crônica; Agulhamento seco; Pontos-gatilho.

ABSTRACT

Pai, Marcus YB. ***Dry needling has lasting analgesic effect in shoulder pain: a double-blind, sham-controlled trial*** **[tese]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2021.**

INTRODUCTION: Myofascial pain syndrome (MPS) affects the majority of chronic shoulder pain patients. Dry needling (DN) is a common treatment option for MPS, but its temporal variation and sensory effects remain unknown. We evaluated in a double-blind, sham-controlled study the pattern of analgesic efficacy and local sensory changes of a single session of DN for MPS in chronic shoulder pain patients. Patients with chronic shoulder pain were randomized into active (n=20) or sham (n=21) groups. A single DN was performed by a researcher blinded to group assignment and pain outcomes. Pain intensity was assessed by the numeric rating score (NRS) and sensory thresholds were evaluated with a quantitative sensory testing protocol (QST), including the area of tactile sensory abnormalities seven days before needling, right before, and seven days after the intervention. RESULTS: DN led to significant larger pain intensity reduction (from 6.30 ± 2.05 to 2.40 ± 2.45 in the active, and from 6.04 ± 1.32 to 5.14 ± 1.49 in the sham group; $p = 0.02$). Pain reduction scores were significantly different on the second day after needling and persisted until the seventh day, and were accompanied by improvement in other dimensions of pain, and by a decrease in the area of mechanical hyperalgesia in the active DN group only ($p<0.05$). CONCLUSION: Active trigger point dry needling provided analgesic effects compared to sham and decreased the area of local mechanical of hyperalgesia. These findings have practical clinical implications and may provide mechanistic insights into the mechanisms behind MPS.

Descriptors: Myofascial pain; Chronic pain; Dry needling; Trigger points.

1 INTRODUCTION

1. INTRODUCTION

Musculoskeletal pain disorders rank as the tenth leading cause of years lived with disability worldwide (Disease et al., 2017). Shoulder pain is responsible for up to 20 percent of musculoskeletal complaints (Urwin et al., 1998; Luime et al., 2004), leading to inability to work, loss of productivity, and a considerable burden for the patient and society (Pribicevic, 2012). Shoulder pain is a common complaint in all ages, and it is one of the major reasons why patients consult with primary healthcare providers (Feleus et al., 2008; Pribicevic, 2012). The lifetime prevalence of shoulder disorders may affect up to 70% of the population (Yeng et al., 2001; Cadogan et al., 2011).

Myofascial pain syndrome (MPS) is characterized by local and referred pain due to the occurrence of tenderness in a taut, palpable band of muscle fibers, where painful hyperalgesic myofascial trigger points (MTrP) are identified by manual palpation (Travell & Simons, 1983; Graven-Nielsen & Arendt-Nielsen, 2010). MTrPs occur due to dysfunctional endplate potential and excessive acetylcholine release in the neuromuscular junction that prevents muscle fibers from fully relaxing. It usually arises from muscle overload secondary to inadequate postures or overuse from repetitive activities or as part of referred pain from deeper injured structures, resulting in increased local tenderness and pain (Gerwin, 2001; Cagnie et al., 2012; Dunning et al., 2014).

MPS is highly prevalent and is considered one of the most common mechanisms behind shoulder disorders, affecting up to 95% of patients (Dommerholt & Fernández-de-las-Peñas, 2013). MPS is frequently found in nociceptive shoulder pain and is thought to be the main cause of pain or coexist and contribute to shoulder pain occurring due to other etiologies, such as subacromial impingement syndrome bursitis, and rotator cuff syndrome (Bron et al., 2011).

MPS is associated with disability and dysfunction due to decreased range of motion of the girdle joints (Bron et al., 2011).

A variety of therapeutic techniques have been proposed to treat trigger points and MPS (Kamanli et al., 2005). Non-pharmacological approaches are widely employed (Yeng et al., 2001) and generally preferred over pharmacological ones due to better tolerance and safer adverse event profiles (Desai et al., 2013). Dry-needling (DN) is a minimally invasive procedure, consisting of the use of a fine, solid filiform needle repetitively inserted into the fascia and muscle in a fan-like technique. Techniques analogous to DN have been used for over a century in Western Medicine (see description from Sir William Osler in *Principles and Practice of Medicine* in 1912 (Gerwin, 2001). DN is believed to cause musculoskeletal pain relief (Travell & Simons, 1983) and improvement in range of motion by triggering a local twitch response (Gal et al., 1991; Annaswamy et al., 2011), subsequently leading to a temporary attenuation or disappearance of MTrPs. The dry needling of myofascial trigger points can result in a mechanical reduction of peripheral nociceptive inputs from the muscles (Cagnie et al., 2012), contributing to peripheral, spinal and supraspinal desensitization, along with activation of multiple central pain regulatory pathways (Dunning et al., 2014), and functional restoration of neuro-myofascial tissues (Cagnie et al., 2012). DN reduces the irritability of neuromuscular junctions (motor endplate noise) (Audette et al., 2004) and sympathetic overactivity in the affected regions, effectively reducing the overlap of the contractile proteins and relaxing the sarcomeres (Shah & Gilliams, 2008). DN is usually performed at active MTrPs (Kamanli et al., 2005; Dunning et al., 2014). It is believed that treatment of the trigger point, and thus removal of the peripheral source of nociceptive stimulus can reduce mechanical hyperalgesia and allodynia, as observed in migraine (Giamberardino et al., 2007) and whiplash (Freeman et al., 2009). Although needling of MTrPs is part of the daily practice of physicians dedicated to the treatment of musculoskeletal pain, there is still limited

clinical evidence for its actual efficacy, as few clinical trials have evaluated its effects in chronic shoulder pain (Ge et al., 2008; Desait et al., 2013) against a proper sham needling (Cummings & White, 2001; Kietrys et al., 2013) and for a sufficient length of time.

The purpose of the present study was to evaluate the actual analgesic effects of a DN session on shoulder pain associated with MPS in a double-blind controlled study. We have also explored the concomitant changes in cutaneous sensory thresholds with a battery of quantitative sensory testing (QST) in the area of referred pain triggered caused by DN (e.g., secondary hyperalgesia reduction) and its potential role in predicting the temporal persistence of the analgesic effects caused by the needling procedure.

2 OBJECTIVES

2. OBJECTIVES

2.1 Main clinical endpoints

Evaluate reduction in pain intensity: average pain intensity over the last 24 hours, seven days after the procedure (D14). Baseline average pain intensity was assessed with the average pain of the 7 days prior to needling (from day 1 until 7 = baseline), on the day of the procedure (D7, before dry needling), and daily on the remaining 7 days (until day 14).

2.2 Secondary endpoints

The secondary aim was to assess whether the analgesia due to dry needling correlated with acute DN-related alterations evaluated in Quantitative Sensory Testing (QST), in mechanical hyperalgesia area and other sensory variables, such as cold-induced pain, mechanical hyperalgesia, or mechanical hyperesthesia.

To evaluate concomitant changes in cutaneous sensory thresholds in the area of referred pain triggered by the needling procedure and its potential role in predicting the temporal persistence of the analgesic effects caused by the needling procedure.

3 LITERATURE REVIEW

3. LITERATURE REVIEW

3.1 Myofascial pain syndrome

Myofascial Pain Syndrome (MPS), a commonly diagnosed musculoskeletal disorder, is a painful condition affecting the muscles and surrounding fascia. It is characterized by regional muscle pain and the presence of myofascial trigger points (MTrPs) in taut bands of skeletal muscles and fascia, consisting of localized and hyperirritable nodules (Travell & Simons 1983, Shah et al., 2015). The MTrPs are typically associated with chronic pain that is radiated or referred, and perturbation may often result in a local twitch response and the replication of referred pain or pain radiation (Gerwin, 2001; Yeng et al., 2010).

MPS is probably the main cause of musculoskeletal pain, affecting up to 95% of patients with chronic pain disorders (Gerwin, 1995), and is also a common finding in pain management centers (Teixeira, 1997). Its consequences in terms of dysfunction, disability and financial loss are great (Hong, 2002). Different studies have demonstrated that myofascial pain trigger points can be associated with several diverse pain conditions, being either the primary source of pain, or a secondary pain condition, in a variety of disorders such as migraine (Giamberardino, 2007), tension-type headache (Do, 2018), temporomandibular disorder (Sarlani, 2004), neck pain (Cerezo-Téllez, 2016), rotator cuff syndrome and shoulder pain (Perez-Palomares, 2009), low back pain (Malanga et al., 2010) and pelvic pain (Srinivasan et al., 2007).

Although muscle overuse and overload were suggested as causing MPS, the exact cause of MPS remains controversial. When the muscle fiber suffers injury, overload, or repetitive stresses, it develops MTrPs, causing exaggerated muscle contraction during a prolonged period. In parallel, muscle fatigue occurs (Bron & Dommerholt, 2012). Focused ischemia and subsequent abnormalities of the extracellular environment of myofibrils, in addition to the

release of algiogenic substances, generate a vicious circle characterized by increased motor activity and the neurovegetative nervous system, increasing sensitivity to pain. Painful events can be auto sustained by central and peripheral sensitization phenomena (Fernandez-de-las-Peñas et al., 2007).

Additionally, multiple abnormalities linked to MPS show their complexity, while obscuring the specific underlying pathophysiological mechanisms: dysfunction in the motor endplate, sustained skeletal muscle contraction with dysfunctional calcium channels; abnormalities linked to the extracellular matrix in the fascia; peripheral and central pain sensitization and associated neurotransmitter abnormalities; localized, neurogenic, and generalized inflammation; microvasculature abnormalities; motor endplate abnormalities; hypoxia and other local biochemical abnormalities (Stecco et al., 2013; Shah et al., 2015; Weller et al., 2018; Tantanatip & Chang, 2020).

MTrPs may be active or latent. Active trigger points generate referred and spontaneous pain, while latent points may produce local or referred pain after mechanical stimulation.

The treatment of MPS consists of the inactivation of MTrPs with the interruption of the vicious cycle pain-spasm-pain (Bron & Dommerholt, 2012) in addition to the removal of causal and perpetuating factors. The control of pain and disability implies the need for physical, psychological, and social rehabilitation, and should include a multidisciplinary team to meet the complexity of each case. Different therapies can be effective in pain management for MPS patients, including ischemic compression, local anesthetic injection, dry needling, botulinum toxin, physical therapy, postural and ergonomic correction. However, due to the complexity and limited understanding of the underlying pathophysiological mechanisms, treatment is individualized and not easily comparable. In particular, dry needling, because of its short- and long-term effectiveness, low cost, and availability, has been considerably recommended as an adjunct treatment for MPS in recent literature (Gerber et al., 2017; Kütük et al., 2019).

3.2 Concepts and History of Myofascial Pain Syndrome

Pain is characterized by being multidimensional, involving a personal and subjective experience. Despite the ongoing clinical interest in pain research and management, pain continues to be a barrier that jeopardizes patients' well-being. Sensitive and cultural aspects can be altered by the socio-cultural and psychic variables of the individual and the environment (Gerwin, 2001). Diagnosis and treatment of pain requires an understanding of this subjective experience that requires awareness, regardless of its severity or the pathophysiological mechanisms involved. Chronic musculoskeletal pain has been characterized as a biopsychosocial disorder in which contextual, cognitive, and emotional factors, as well as biological factors, all influence pain perception significantly (Galasso et al., 2020).

Although MPS is one of the most common causes of pain and disability in patients with musculoskeletal pain, many health professionals and patients do not recognize it, as the diagnosis depends exclusively on the clinical history and the findings of the clinical examination (Gerwin, 2001). Many patients are treated as having bursitis, arthritis, or visceral diseases, with no significant improvement in the clinical condition.

The concept of musculoskeletal pain has evolved throughout history (Cummings & Baldry, 2007). European medical literature has been describing the clinical entity of painful muscles with nodules under different names for many centuries. Guillaume de Baillou was the first to describe musculoskeletal pain in 1600. Balfour went on to say that the discomfort was caused by "thickenings" and "nodular tumors" in 1816. Froriep identified the TPs as a set of painful connective tissue in 1843. Kellgren, a British rheumatologist, used intramuscular hypertonic saline injections to study and identify patterns of referred pain in various muscle groups. In 1816, Balfour identified thickened painful nodules. He also observed the occurrence

of the patient's painful reaction when he was stimulated by the painful point. which later became known as the jump signal (Bennett, 2007). Trigger points have been called several terms since then: fibrosis myofasciitis, muscular rheumatism, rheumatic myositis, myogelosis, myalgia, myofascial pain, and so on. After several decades of extensive research, MPS is still an enigmatic disorder (Shah et al., 2015). After 1930, there were advances in the understanding of physiopathology, diagnosis, and treatment of MPS. Local and referred pain was charted after injection of hypertonic saline into various anatomical structures such as fascia and muscle. These concepts were brought together by an American physician - Janet Travell and his colleagues, who described their findings via multiple works, the most notable of which are two volumes of *Myofascial Pain and Dysfunction – The Trigger Point Manual*. These books are often credited with the first official description of this condition as MPS, as well as the proposals of key involvement of myofascial tissues in MPS - MTrPs as a central feature of the MPS, and the creation of an MTrPs-based treatment (administration of injections into MTrPs) (Travell & Simons, 1983; Bennett, 2007). The authors redefined the trigger points as circumscribed deep tender points, with a localized contractile response when pressed or stimulated, that generated referred pain.

This earlier manual, along with more than 40 papers Travell published on the topic, was critical in defining and popularizing MPS and MTrPs diagnosis and treatment among the medical community. MPS is now used to refer to a particular condition that differs from other soft tissue pain conditions such as fibromyalgia, polymyalgia rheumatica, or arthritis (Gerwin, 1999). It also manifests as local pain with referred pain and increased tension and reduced muscle strength and flexibility.

Other important clinical features of MPS include motor (muscle weakness, stiffness, and limitation of range of motion) and autonomic (vasoconstriction or vasodilation and piloerection) components (Gerwin, 2001).

3.3 Epidemiology

The prevalence of SDM in the population is difficult to determine, since the diagnostic criteria are clinical and depend on the finding of trigger points and bands of tension, requiring training by the professional to identify them. It is also necessary to exclude associated conditions or underlying disorders of the painful myofascial syndrome. However, it has been estimated that approximately 9 million citizens in the United States, which is about 3% of the general population in the US, may have MPS, with the risk being considerably higher in the older age group (Malanga et al., 2010).

However, a survey estimated the prevalence among people visiting internal medicine clinics for some reason was higher than that of the general population, at about 10% (Skootsky et al., 1989). In the same report, the prevalence of MPS for those who visited with the primary symptom of pain was even higher, at 30%.

Furthermore, research from pain clinics worldwide has repeatedly shown that patients with chronic pain syndromes have a much higher occurrence of MPS than the general public or people visiting internal medicine clinics (Bourgaize et al., 2018). In several experimental studies on patients with chronic headache syndromes, over 50% of the patients had active MTrPs in the head (Do et al., 2018). Similarly, the occurrence of active MTrPs in patients with neck and shoulder pain syndromes in the corresponding painful areas was greater than 40% (Ribeiro et al., 2018). Significantly increased rates of MPS have also been identified in the context of cancer pain (Castro-Martín et al., 2020; Vulfsons & Minerbi, 2020).

Risk factors for MPS include age, female sex, psychological factors including higher levels of stress and anxiety (Velly et al., 2003; Dommerholt et al., 2006). Furthermore, it has been proposed that patients with insomnia are more prone to develop MPS than healthy controls (Lin et al., 2017). In addition, a high risk of MPS has been indicated for various

hormonal and nutritional deficiencies e.g., hypothyroidism, deficiency of vitamin D, deficiency of iron, and deficiency of vitamin B12 (Dommerholt et al., 2006). Other risk factors proposed for MPS include inactivity, abnormal posture, mechanical and psychological stress, and structural imbalances, including deformities of the limb length (Bennett, 2007).

The varying prevalence of myofascial pain in different studies may be due to the difference in the populations studied, the degrees of pain chronification, and the absence of a standardized criteria for the diagnosis of trigger points and the variation in awareness of the diagnosis and diagnostic skills of examiners (Yap, 2007; Tantanatip & Chang, 2020).

3.4 Etiology

The pathophysiology of MPS is not completely understood (Bennett, 2007). Numerous mechanisms, including eccentric overload, submaximal sustained and submaximal concentric contractions, may be involved (Hong, 2002; Malanga et al., 2010). Sustained muscle lesions, including microtrauma due to repetitive work-related and overuse-related microtrauma, associated with muscle ischemia or vascular remodeling, are possible causes of local pain and perpetuation of trigger points (Bron & Dommerholt, 2012). Sustained abnormal activation of muscle contraction-related proteins or signaling pathways can lead to the development of MTrPs (Jin, 2020). Neuromuscular alterations, such as abnormal acetylcholine transmission at the motor endplate, resulting in peripheral pain have been described as potential causes (Gerwin, 2004).

Local myofascial pain is caused by the release of substances from damaged muscle, such as adenosine triphosphate (ATP), bradykinin (BK), 5-hydroxytryptamine (5-HT, serotonin), prostaglandins, and potassium (K+), as well as from the extracellular fluid surrounding the MTrP, such as protons (H+) from the acidic milieu created by ischemia and

exercise (Gerwin, 2004; Shah et al., 2015). These substances elicit the activation of muscle nociceptors and the release of calcitonin gene-related peptite (CGRP) from the motor nerve terminal and from muscle fibers (Gerwin., 2010).

Thus, both a motor and sensory dysfunction may be present. Since MPS is a pain syndrome that involves the muscles and fascia, derangements in the nervous system, muscular system, and fascia (connective tissue), may independently trigger and sustain the MPS. Although earlier authors initially believed that the muscular system (muscle overuse) was the primary cause of MPS, recent findings reveal a high likelihood of additional neurogenic and fascial causes (Fernandez-de-Las-Penas et al., 2007).

Untreated trigger points can evolve with an irritable focus and persistent pain impulses by a sensitive neuron to the spinal cord, which may result in an increase in the release of nociceptive neurotransmitters and a lower threshold for synaptic activation, contributing to the amplification and perpetuation of pain. This condition can affect sensory, motor and sclerotomal components of the spinal segment, making it hyperactive and hyperexcitable, resulting in physical manifestations such as dermatomeric sensitization with increased skin thickness and the affected area becomes painful and myotomal sensitivity in the muscles innervated by the segment spinal sensitivities with hypertonicity and spasms in MTrPs (Yap, 2007).

3.5 Signs and Symptoms

The most common symptom in most MPS patients is chronic localized, regional, or referred muscle pain, which often includes the following features: i) pain mostly lacks a known inciting factor, ii) pain is typically non-dermatomal in distribution, iii) pain usually worsens and produces referred pain or referred tenderness on compression or movement iv) pain often

results in a range of motion limitations (Alvarez & Rockwell, 2002). However, MPS is becoming more widely recognized as a new cause of acute muscle pain necessitating emergency room visits (Shah et al., 2015).

Although any group of muscles may be involved in MPS, the muscles most involved are those in and around the spine (cervical and lumbar); shoulder, including upper and mid-back; and pelvic regions, including the low back; while the involvement of the muscles of the head, including the temporomandibular region; thighs; calves; and forearm is also common (Alvarez & Rockwell, 2002; Bennett, 2007). However, recent expert consensus indicates that the nature of pain may also be defined as burning, tingling, sharp, or spreading (Fernández-de-Las-Peñas et al., 2018).

In addition to pain, patients with MPS can experience a range of symptoms, including motor, sensory, and autonomic symptoms. The motor symptoms include muscle weakness without atrophy, stiff muscles, and range of motion limitations (Dommerholt et al., 2006; Bourgaize et al., 2018). Sensory symptoms include hyperalgesia, allodynia, paresthesia, and decreased pain thresholds, also in the overlying skin area (Dommerholt et al., 2006). Lacrimation, diaphoresis, flushing, pilomotor changes, and temperature fluctuations are examples of autonomic symptoms (Dommerholt et al., 2006; Bourgaize et al., 2018).

A connection between MPS and psychological symptoms has recently been proposed. The research found that patients with MPS had a higher proportion of neuroticism and anxiety symptoms (San-Antolín et al., 2020), while another study revealed an association with mood alterations (Shah et al., 2015). More study, however, is needed before any conclusions can be drawn in this regard.

The two most prevalent signs of MPS elicited during palpations, which are also considered to define MPS, are the presence of one or more taut bands and hard/nodular MTrPs in those bands of the muscle affected that are generally defined as hyperirritable/tender spots

or nodules within the taut muscle band, which may or may not be spontaneously painful (Fernández-de-Las-Peñas & Dommerholt, 2018).

While most MPS patients have spontaneously painful single or multiple MTrPs within the taut muscle bands, which are known as active MTrPs, some patients may have latent MTrPs, which only produce pain on palpation, i.e., are typical without spontaneous pain in that region and do not recreate the patients' symptoms; additionally, latent MTrPs may be found in entirely asymptomatic or normal patients (Bennett, 2007).

Furthermore, palpation combined with sustained mild pressure or needling of the MTrPs for a few seconds can elicit a variety of responses, including a local twitch response, replication of a non-dermatomal but a myotomal referred pain, or pain radiation, and even a jump sign, which refers to the patient's involuntary disproportionate flinching (Alvarez & Rockwell, 2002; Bennett, 2007; Shah et al., 2015; Tantanatip & Chang, 2020).

3.6 Peripheral and Central Sensitization in Myofascial Pain Syndrome

Sensitization is the process of reacting to a stimulus with hypersensitivity, also known as hyperstimulation. Sensitization to pain entails multiple neurological changes, including a decrease in nociceptive pain threshold in afferents and disproportionate activation of ascending pain pathways, including the dorsal root ganglion and wide-range interneurons, resulting in field widening and referred pain; disinhibition in the brain-stem descending pain inhibitory pathways, as well as functional plasticity in the thalamus and pain cortex, including the insula and limbic cortex, are followed by a slew of biochemical, neurophysiological, and other molecular alterations at each stage (Bennett, 2007; Shah et al., 2015).

Although peripheral sensitization is described as a decrease in pain threshold at the nociceptive level and the generation of pain impulses by non-pain related broad afferents (Ge

et al., 2011); that affecting the dorsal root ganglion, which is a major information exchange point, is referred to as segmental sensitization, which is often considered a part of central sensitization; and that affecting the levels above the dorsal root is referred to as central sensitization (Shah et al., 2015; Suputtitada, 2016).

It has been proposed that pain occurring in myofascial tissues is more capable of causing sensitization than pain originating from the skin (Bennett, 2007). The majority of MPS patients exhibit normal sensitization symptoms such as hyperalgesia, allodynia, referred pain or extended receptive pain fields, and increased pain sensitivity with the same stimulus over time. As a result, peripheral and central sensitization has been strongly linked to MPS in recent decades, and even a neurogenic hypothesis has been proposed, implying that MTrPs are generated secondary to neural dysfunction and sensitization; however, whether primary or secondary or even both, peripheral and central sensitization are likely to be one of the underlying causes of MPS (Teixeira, 2001; Ge et al., 2011).

The molecular mechanisms for MPS-mediated sensitization include, but are not restricted to low pH; elevated nerve growth and cytokines like interleukins; and elevated neurotransmitters such as substance P, glutamate, calcitonin gene-related peptide, serotonin, and norepinephrine; acetylcholine-related dysfunction at motor endplates; and mast cell dysfunction at MTrPs (Shah et al., 2015; Suputtitada, 2016; Vadasz et al., 2020).

Shah, Phillips, and Gerber developed a microdialysis instrument to assess, in real time, the biochemical characteristics of the muscle. Three groups were selected with 3 volunteers each: group 1) normal, group 2) with latent PG on trapezoid and group 3] with active MTrPs on trapezoid. The concentration of H+, BK, SP, CGRP; TNF-α, IL-l β, 5-HT and NA were significantly higher in group 3 than in the other two. pH was significantly lower in group 3. After local muscle dry needling procedure, the authors found a decrease in the concentrations of CGRP and SP in the active trigger point (Shah, 2008).

The clinical implications of pain sensitization on MPS emerge in many aspects. Sensitization was proposed not only to initiate but also to propagate and maintain MPS, especially in the context of comorbid chronic pain conditions (Shah et al., 2015; Aredo et al., 2017). In addition, pain associated with sensitization has been suggested to be challenging to treat than otherwise (Bennett, 2007). It was further proposed that sensitization is associated with even latent MTrPs and those without acute pain (Shah et al., 2015; Vadasz et al., 2020).

Thus, some authors suggested that pain circuit breakdown or MTrPs be inactivated with desensitization therapy, including dry needling for patients with MPS (Chou et al., 2012; Fernández-de-las-Peñas & Dommerholt, 2014; Aredo et al., 2017; Fernández-de-Las-Peñas & Nijs, 2019). Furthermore, some authors advise a regular sensitization assessment in MPS patients (Shah et al., 2015; Suputtitada, 2016; Aredo et al., 2017).

3.7 Diagnosis

Myofascial pain syndrome is a disorder that is often misdiagnosed and overlooked. MPS is diagnosed based on a thorough medical history and physical examination. A detailed history of the clinical condition, especially highlighting the occurrence or not of: musculoskeletal overloads, inadequate postures adopted during the execution of tasks (sleep, leisure, activities at home, at work and sports), on personal and family background, emphasizing previous traumatic, inflammatory, metabolic, oncological, neuropathic or musculoskeletal disorders and a broad physical, physiological and neurological examination, focusing attention on the inspection of the attitudes, postures, conformation and movement pattern of the muscular structures and asymmetry of the limbs, are fundamental for the diagnosis (Bennett, 2007).

A history of regional muscular pain in myotomal distribution and a clinical review that shows taut bands comprising hyperirritable spots or nodules i.e., MTrPs [Major criteria per the Trigger Point Manual]. MTrPs are widely regarded as the hallmark of MPS. A trigger point can be found by palpating a solid, hypersensitive nodule that causes a local twitch response and radiating pain when local pressure is applied to it during an inspection. Sensory alterations such as paresthesia, dysesthesia, and localized excessive skin tenderness may also be associated with referred pain (Fernández-de-Las-Peñas & Dommerholt, 2018).

Other test anomalies can include replication of pain and local twitching at compression or perturbation, jump signs, decreased motion range, and muscle fatigue without apparent wasting [Minor criteria per the Trigger Point Manual] (Gerwin, 2014). However, the physical assessment and clinical diagnosis is not always clear, as the location of the MTrP site may also be a significant predictor of reliability, as MTrP frequently forms deep within the paravertebral muscles, making them extremely difficult to detect solely by manual palpation (Srbely et al., 2016).

Localized pain can be documented and quantified with the use of pressure algometers: the pressure required to induce pain should be less than 2 kg/cm^2 in relation to the contralateral non painful normal points (Park et al., 2011).

A standard laboratory test or imaging technique for MPS does not exist. Trigger points can be associated with focal hypoechogenic areas in chronic MPS in ultrasound imaging. Diagnostic ultrasound has been recently used as a noninvasive real-time imaging tool to evaluate muscle, tendon, fascia, blood vessels and other soft tissues, with possible evaluation of viscoelastic properties of myofascial tissue. Surface electromyography may present spontaneous and increasing electrical activity over MTrPs, with motor dysfunction of the myofascial tissue. (Dommerholt et al., 2006; Cojocaru et al., 2015; Rivers, Garrigues, Graciosa & Harden, 2015; Tantanatip & Chang, 2020).

A range of other imaging techniques are widely used in the research context, including magnetic resonance elastography, with a taut band in chevron pattern, and infrared thermography, a non-invasive diagnostic imaging technique that evaluates long infrared radiation emitted by human skin (Nahm, 2013). Thermography findings may include hyper-radiation presence in regions of higher muscle tension when compared to healthy unaffected opposing muscles, and higher temperature in cooler MTrP areas. There is still, however, a lack of standardization in infrared myofascial muscle analysis (Dibai-Filho & de Jesus Guirro, 2015). Some circulating biomarkers, such as cytokines and growth factors, have also been suggested but their clinical utility remains uncertain, and further research is needed to encourage their clinical use (Srbely et al., 2016).

Numerous illnesses may share a clinical manifestation with MPS, but the most prominent characteristics include: other regional pain syndromes, such as chronic pelvic pain and headache syndromes; soft tissue inflammatory conditions, such as fibrositis, tendinitis, and bursitis; nerve entrapment syndromes; and another myofascial condition, fibromyalgia, which traditionally manifests with widespread pain and systemic symptoms, and when examined, can show hyperextensibility in the joints and multiple diffuse tender points that cannot be easily distinguished from MTrPs (Ge, 2010).

Furthermore, the identification of structural predisposing triggers in MPS patients may necessitate radiographic examination, while nutritional/hormonal deficiencies may necessitate laboratory testing; similarly, anxiety and psychosocial stress may necessitate a psychiatric evaluation (Tantanatip & Chang, 2020). Due to the restricted clinical applicability of the diagnostic technology, physical examination remains the most accepted form of evaluating myofascial trigger points.

3.8 Treatment of Myofascial Pain Syndrome

MPS therapy involves several objectives. They include the symptoms of relief, management of inciting/aggravating factors and co-morbid pain syndromes, promotion of peripheral and central desensitization, the transformation of active MTrPs into latent points (inactivation of MTrPs), support for social and occupational rehabilitation and integration, restoration of healthy lifestyle and posture and, finally, patient education and self-care (Hong, 2006; Yap, 2007).

MPS treatment may be categorized as conservative or non-intrusive, such as manual therapy, spray and stretch therapy, and physical therapy, and aggressive or invasive, such as MTrPs injections, dry needling, and acupuncture (Hong, 2006). It may also be categorized as non-pharmacological with various non-drug-based therapies that are gaining wide acceptance, and pharmacological such as analgesics, anesthetics, muscle relaxants, anti-convulsants, anti-depressants, and neurotoxins (Hong, 2006; Desai et al., 2013).

The inactivation of MTrPs, which could be attained in a variety of ways, such as dry needling, acupuncture, trigger point injection, and transcutaneous electrical nervous stimulation (TENS) was suggested as an efficient approach to the treatment of MPS and thus is a cornerstone in MPS therapy, especially in the management of those with chronic symptoms (Desai et al., 2013; Galasso et al., 2020). The mechanical inactivation of MTrPs disrupts abnormal muscle fibers or nerve endings that perpetuate the trigger point activity (Yap, 2007).

However, even though the clinical efficacy of the inactivation of MTrPs is high, MPS management has been recognized as a continuing clinical difficulty with unimodal treatment, particularly in patients with severe and prolonged symptoms (Galasso et al., 2020). Instead, combination therapy approaches might provide better outcomes. In most patients with MPS, multi-modal approaches with repeated therapy sessions seem to be effective in achieving the treatment goals, but some of them do have unsatisfactory outcomes (Segura-Pérez et al., 2017).

Newer evidence with more patient-participatory approaches has shown that a comprehensive patient-centered approach may lead to a high rate of functional restoration in most MPS patients (Desai et al., 2013). In addition, comprehensive pain-management approaches have been proposed as reducing long-term morbidity associated with MPS (Hong, 2006). The inadequate management of the causative factors was proposed as a neglected cause of treatment failure (Tantanatip & Chang, 2020).

3.8.1 Oral and Topical Pharmacological Treatment

Pharmacological treatment, including both oral or topical drugs, are widely accessible, and frequently used in clinical practice for symptomatic relief in MPS and chronic pain treatment, particularly when the symptoms are acute or highly aggravating, (Fleckenstein et al., 2010). For analgesia, common analgesics, anti-inflammatories, muscle relaxants, and weak opioids are used (Borg-Stein & Simons, 2002). For chronic pain MPS and associated symptoms, some classes of antidepressants and anticonvulsants are commonly used (Gerwin, 2010).

However, few limited clinical trials, conducted over brief periods, have evaluated the effectiveness of pharmacological agents in MPS (Desai et al., 2013). As a result, pharmacological treatment should be thought of as an adjunct treatment as part of multi-modal treatment, and long-term pharmacological treatment for MPS may not be suitable (Gerwin, 2010).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for acute pain since they are inexpensive and have a low risk of side effects. There is compelling evidence that NSAIDs' analgesic properties alleviate pain in acute musculoskeletal (MSK) disorders. Given the high degree of overlap between MPS and MSK pain, it seems reasonable to consider

NSAIDs as an initial treatment option for both disorders. On the other hand, long-term use should be approached cautiously due to the gastrointestinal, renal, and antiplatelet side effects (Gerwin, 2010).

In patients with chronic pain due to MPS, tricyclic antidepressants and anticonvulsants are commonly used, due to their pain modulation at central level. Tricyclic antidepressants modulate central serotonergic and noradrenergic signals, possibly reducing neurotransmission of painful stimuli (Desai et al., 2013).

While several drug classes of orally active pharmaceutical agents have been evaluated in patients with MPS, the effectiveness of one over other has not been identified (Gerwin, 2010; Desai et al., 2013). Therefore, the choice of agent may be individualized according to the patient's characteristics, such as symptom severity, tolerance, and comorbid medical conditions or pain syndromes (Yap, 2007; Desai et al., 2013;).

3.8.2 Trigger Point Injections with Anesthetic Agents, Steroids, or Normal Saline

Local anesthetics can be used to inactivate MTrPs through a variety of mechanisms, including peripheral desensitization, vasodilation, and altering motor endplate potential. Steroid supplementation can provide additional benefits by reducing peripheral and central desensitization. In a few studies, saline-only MTrPs injections were also shown to inactivate MTrPs, but the underlying mechanism is unclear (Ting et al., 2020).

Inactivation of MTrPs by injections containing anesthetic agents with or without steroids is often regarded as an efficient treatment strategy for MPS in patients who have failed conservative treatment, and this could benefit by not only reducing pain but also expediting functional improvements and attaining analgesic dose reductions (Hong, 1994; Walker & Shah, 2020). This approach is less expensive and has a lower incidence of post-injection muscle

soreness than MTrPs inactivation through botulinum toxin or dry needling. Based on these advantages, this approach has been suggested as the first-line trigger point injection therapy in the subgroup of MPS patients who have failed conservative treatment (Walker & Shah, 2020). Saline-only injections were also prescribed as a first-line injection therapy because of similar advantages (Ting et al., 2020).

Multiple regimens of local anesthetics with or without steroids (triamcinolone) have been reported to be effective, with dosages ranging from 0.5 cc to 10 cc administered at varying intervals and frequencies (Ting et al., 2020). While there is no specific injection protocol, one author suggested using a low dose of a low-concentration local anesthetic, such as 0.5 to 1.0 cc of 0.5% procaine or lidocaine per MTrP, to produce the desired effects with minimal muscle fiber damage and to prevent other procedure-related complications (Hong, 1994). Furthermore, it has been proposed that the injection should be administered rapidly to key active MTrPs based on clinical discretion, with a swift insertion of the needle at several sites in the MTrP until a local twitch response is elicited, and only then should the anesthetic be administered (Hong, 1994). Caution should be exercised, and hemodynamic monitoring may be required, even though the injections are generally safe, however, it is important to note that being a invasive intervention, the trigger point injection could lead to complications, including infection, bleeding, allergic reaction, hematoma, vessel injury and pneumothorax (Chim & Cheng, 2009; Hammi et al., 2020).

To minimize the risk of complications, ultrasound has been recently used in clinical practice to determine the location and depth of MTrPs, enhance needle visualization, and even direct the procedure in real-time, resulting in an improved safety profile (Botwin et al., 2008; Chim & Cheng, 2009; Niraj, Collett & Bone, 2011). Furthermore, recent research revealed that ultrasonography-guided injections outperformed non-ultrasonography-guided injections in terms of efficacy (Kang et al., 2019).

Interestingly, MTrPs injections' clinical effectiveness may be influenced by several factors. Pre-injection anxiety, for example, has been shown to have a negative impact on clinical response in MPS patients (Healy et al., 2015). Another study observed that patients who had comorbid fibromyalgia had a lower and slower clinical response than those who did not have fibromyalgia (Hong & Hsueh, 1996). A survey on 191 patients investigated the variety of factors that contributed to treatment failure with trigger point injections. According to the findings, unemployment, prolonged pain length, and a decrease in social behavior were all predictors of treatment failure (Hopwood & Abram, 1994). It was also suggested that the following conditions be regarded as possible contraindications: fibromyalgia, unmanaged psychiatric disorders, needle-phobia, anesthetic allergies, anticoagulant usage, pregnancy, and history of keloids (Hammi et al., 2020).

3.8.3 Injections with Botulinum Toxin A

Injection of botulinum toxin A, a neurotoxin that suppresses the presynaptic release of acetylcholine at the neuromuscular junction, leads to dose-dependent chemical denervation and muscle relaxation that can last for months (Colhado et al., 2009; Rivera-Día et al., 2014). Furthermore, intramuscular botulinum toxin injection decreases acetylcholine-dependent afferent signals in the muscle spindle (Casale & Tugnoli, 2008; Kütük et al., 2019).

Botulinum toxin injection has been proposed to achieve analgesic effect in chronic muscle pain through the following mechanisms: reduced intramuscular neurovascular compression and ischemia; reduced nociception and peripheral desensitization, especially that facilitated by group 3 and 4 afferents; and inhibition of other neuropeptides, including substance P and glutamate, and neurogenic inflammation (Desai et al., 2013; Rivera-Día et al., 2014). These proposed analgesic mechanisms may be important to the function of botulinum

toxin injection in MPS patients by generating therapeutic sarcomere relaxation, nociceptive inhibition, and peripheral desensitization (Casale & Tugnoli, 2008; Climent et al., 2013).

However, the clinical evidence for botulinum toxin's effectiveness in MPS is mixed. While some open-label and a few blinded trials have demonstrated significant clinical benefits; several sham-controlled trials have shown limited clinical benefits that were not considerably different from those produced by placebo, other injectates, or dry needling. On the other hand, a few trials have demonstrated superiority over other injection interventions; and, importantly, no trial indicated a total absence of clinical benefits (Cheshire et al., 1994; Ho & Tan, 2007; Climent et al., 2013). Various factors, such as dose heterogeneity, injection methods, and sample size, may account for these findings. As a result, a Cochrane review and a clinical effectiveness review concluded that the existing evidence of botulinum toxin's clinical effectiveness in MPS is inconclusive, and further studies with better-designed trials is required (Khalifeh et al., 2014; Soares et al., 2014).

Nonetheless, botulinum toxin has been proposed as a promising therapeutic alternative for patients with refractory MPS who have exhausted all other possible therapies (Climent et al., 2013; Desa et al., 2013). It has also been proposed as a potential treatment alternative for MPS patients who have comorbid nephropathy or impaired renal function, as well as those who have comorbid pain syndromes affecting the head, such as temporomandibular dysfunction and migraine (Colhado et al., 2009; Gandolfi et al., 2018).

However, there are many drawbacks to its prevalent clinical usage, including the high cost of treatment, which can be particularly prohibitive in resource-constrained contexts. Its use is still considered off-label, and is not included in most insure plans for reimbursement. Furthermore, it can be considered an experimental therapy, and the use of botulinum toxin can require informed consent in certain clinical practices (Casale & Tugnoli, 2008; Ting et al. 2020). Furthermore, the botulinum toxin dose per MTrP is not specific, with researchers

reporting doses ranging from 10 to 40 IU per MTrP depending on muscle size (Göbel et al., 2006; Chaurand et al., 2020;). Finally, there could be more side effects than with other injectates, such as muscle weakness and temporary paralysis, particularly in the first few days (Climent et al., 2013; Desai et al., 2013).

3.8.4 Treatment Approaches Focusing on Rehabilitation via Physical Therapy

Physical therapy is one of the main modalities in treating myofascial pain syndrome (Desai et al., 2013). Rehabilitation techniques aims to improve and optimize the muscle mechanical activity, reducing muscle spasm and taut bands, provide recovery of fascia and muscle expansibility, improvement of muscle fatigue and correct causal biomechanical perpetuating factors. Passive, active-assisted and assisted techniques can be used, to recover muscle functionality, muscle trophism, to decrease muscle tension and cause MTrPs inactivation (Hou et al., 2002).

Multiple physical therapies modalities, either alone or in combination, may be used to achieve functional recovery in MPS patients, based on availability, experience, and patient preferences. Manual or manipulative therapy, including myofascial release, stretch, and spray; kinesiotherapy, including local stretching and strengthening exercise therapy; Kinesio taping; ultrasound; electrotherapy, including TENS; cryotherapy; heat therapy; microwaves; laser; ischemic compression; pulsed radiofrequency energy; and magnetic therapy are among the most prominent approaches (Hou et al., 2002; Desai et al., 2013; Cho et al., 2017).

However, manual therapy and muscle stretching and strengthening exercises remain the mainstays of physical therapy due to their high efficacy (Table 1), ease of availability, and lack of the need for costly equipment and training required for other approaches (Desai et al., 2013).

Numerous reports have evaluated the effectiveness of various physical therapy approaches in the treatment of MPS. A significant number of systematic studies on the effectiveness of physical therapy approaches in MPS have recently been reported; however, the effectiveness of one approach over another remains unknown (de las Penãs et al., 2005; Diz et al., 2017; Ahmed et al., 2018). Another significant finding is that most studies have demonstrated their mild, short-term, and medium-term efficacy, mostly in pain reduction, but some have also concentrated on range of motion and other outcomes (Xia et al., 2017). Furthermore, though manual therapy, local exercise, and electrotherapy have been shown to be efficient, ultrasound appears to be regarded as a technique of doubtful effectiveness (Rickards, 2006; Xia et al., 2017).

Furthermore, there has been a recent rise in publication interest in extracorporeal shockwave therapy (ESWT) (Kobayashi, 2018; Yoo et al., 2020; Zhang et al., 2020; Jun et al., 2021). ESWT uses mechanical pressure waves, that propagate within the muscular tissue, and may increase perfusion, stimulate angiogenesis, and modulate pain signaling in ischemic tissues (Ramon, 2015).

Table 1 summarizes the key findings of the systematic reviews included in this literature review.

Table 1. Key Findings of Systematic Reviews on Effectiveness of Physical Therapy Techniques in Myofascial Pain Syndrome

Physical Therapy Intervention(s)	**Findings of Systematic Review**	**Author(s), Year**
Laser; TENS; Ultrasound;	- Immediate effectiveness with TENS - Short-term effectiveness with Laser - Ultrasound not effective than placebo	Rickards, 2006

Manipulation; Ischemic Pressure; Laser; Electrotherapy; Magnet Therapy;	- Immediate effectiveness with manipulation - Immediate effectiveness with ischemic pressure - Strong effectiveness with laser - Moderate effectiveness with TENS - Moderate effectiveness with magnet therapy	Vernon & Schneider, 2009
Ultrasound	- Insufficient evidence to consider ultrasound as an effective treatment	Xia, Wang, Lin, Cheng & Li, 2017
Stretching and Strengthening Exercise	- Small-to-moderate analgesic benefit in the short term with local exercise therapy - A combination of stretching and strengthening exercises provides higher benefits	Diz, de Souza, Leopoldino & Oliveira, 2017
Kinesio Taping	- Effective analgesic benefits, both alone or in combination with other techniques.	Alotaibi, Ayoub, King & Uddin, 2018
Manual Therapy	- Moderate evidence of effectiveness	Charles et al., 2019
TENS	- Effective at pain relief	Ahmed, Haddad, Subramaniam, Khattab &

		Kumbhare, 2019
Manual Therapy	- Effective in Short-to-medium term	Lew, Kim & Nair, 2020
Stretching and Strengthening Exercise	- May be an effective treatment	Guzmán-Pavón et al., 2020
Extracorporeal Shockwave Therapy	- Effective as an adjunct therapy	Kobayashi, 2018; Zhang et al., 2020
Extracorporeal Shockwave Therapy	- Effective in short term pain relief	Yoo, Oh, Chun, Lee & Lee, 2020
Extracorporeal Shockwave Therapy	- Focused shockwave therapy more effective than other techniques	Jun, Park, Chae & Suh, 2021

Although physical therapy is still mostly thought of as an adjunctive treatment for MPS, few studies have conducted head-to-head comparisons of physical therapy approaches with other types of treatment. Interestingly, several such studies have shown that physical therapy approaches are as effective as invasive treatments like trigger point anesthetic injections and dry needling, emphasizing the essential role that it may play in the rehabilitation of MPS patients (Campa-Moran et al., 2015; Lugo et al., 2016).

3.8.5 Newer Approaches for the Treatment of Myofascial Pain Syndrome

Multiple recent MTrP and non-MTrP treatment approaches that may appear as promising alternatives are being evaluated for MPS, particularly in refractory MPS. However, they must be subjected to stringent evaluation before being accepted as viable treatments for MPS. Nonetheless, the corresponding clinical evidence for these treatments makes them merit consideration.

The injection of Ozone into MTrPs is one of the MTrPs-based treatment approaches. Ozone injections, which are available as a solution of oxygen and ozone, have been studied in many clinical trials of chronic pain syndromes such as spondylosis, osteoarthritis, and shoulder disorder in recent years (Lopes de Jesus et al., 2017; Raeissadat et al., 2018, a). While the precise mechanism of ozone in chronic pain states is uncertain, several theories have been suggested such as phosphodiesterase A2 inhibition, free radical reduction, enhanced oxygenation, and anti-inflammatory impact (Raeissadat et al., 2018, a). A new clinical trial compared the effectiveness of ozone injections in MPS patients with chronic non-specific neck pain to dry needling and anesthetic injection. The report discovered that ozone injection had significant benefits similar to the other two approaches (Raeissadat et al., 2018, b).

Another intriguing MTrPs-based technique that may hold some potential for treating MPS is dextrose injection in the MTrPs, which induces tissue damage and acts as a proliferative agent, eventually triggering tissue repair remodeling. It has also been used as part of a combination prolotherapy regimen to manage chronic pain syndromes (Jensen et al., 2005; Chou et al., 2020). A clinical trial in Korea and a recent case series from Taiwan both demonstrated that dextrose injections had good clinical efficacy in MPS, notably in refractory MPS (Chou et al., 2020; Kim et al., 1997).

In addition to the strengthening/stretching exercises that are well established as a complementary treatment for MPS among the non-MTrPs based treatment approaches, aerobic

exercise is encouraged not only for a generally healthier lifestyle but also as a promoter of central desensitization and an increased pain threshold (Ahmed et al., 2018). Furthermore, aerobic exercise can help to reduce systemic inflammation while also improving blood flow and oxygen supply in the tissues. As a result, it was proposed that these results could translate into a major and cost-effective advantage for MPS patients (Ahmed et al., 2018).

In accordance with this, a research investigated the efficacy of aerobic swimming exercise, also known as low-intensity water-physical therapy, in breast cancer patients with MPS. After 8 weeks of exercise, there was a decline in the number of active MTrPs and a significant reduction in pain among the survey respondents, suggesting that the intervention was efficient (Cantarero-Villanueva et al., 2012). Another research focused on Yoga for patients with chronic neck pain due to MPS and found that regular practice of this exercise resulted in substantial clinical improvements in range of motion and pressure pain threshold after 4 weeks (Sharan, 2014).

Another intriguing non-MTrPs-based non-pharmacological approach to MPS has been connected to the function and biomechanical correction of the postural configuration since irregular posture has been linked to MPS (Tantanatip & Chang, 2020). A survey evaluated the effect of forward head posture and its correction as an adjunctive treatment in MPS and discovered additional advantages after 3 months in the group that received head-posture correction (Iaroshevskyi et al., 2019). Another one-year clinical trial investigated the function of cervical sagittal configuration and used the denneroll orthotic device as an intervention. The research discovered that there were consistent benefits of pain reduction and functional improvements in the intervention group after 10 weeks and up to 1 year (Moustafa et al., 2018). Patients who are proactive in their rehabilitation treatment become more aware of their habits that lead to physical inefficiency and tension in the body (Sharan, 2014).

3.9 Function of Dry Needling in Myofascial Pain Syndrome

Myofascial trigger point dry needling (MTrP-DN) is a neuro-myofascial stimulation technique that is applied directly to the MTrPs to inactivate them. MTrP-DN has been increasingly used as a treatment for MPS over the past few decades (Gerber et al., 2017; Lew et al., 2020).

MTrP-DN refers to the intervention of rapidly injecting a fine needle into the site of the MTrP through the skin – without administering an injectate – in order to inactivate the MTrP and achieve therapeutic benefits, interrupting the pain-spasm-pain vicious cycle, with rapid pain relief and functional restoration, though some medium-to-long-term benefits can also be experienced by patients receiving MTrP-DN (Kaljic, 2018; Fernández-de-Las-Peñas & Nijs, 2019). The mechanical inactivation of the MTrP can reduce the sustained focal muscle fiber contraction (Yeng et al., 2001).

Many operational benefits can be attributed to the MTrP-DN procedure, these are: i) Though invasive, risks are relatively low provided healthcare professionals recognize the limitations of working in safe-needling zones and follow standard procedural precautions; ii) It does not necessarily require sophisticated equipment and has usually lower costs; iii) As a treatment approach for MPS patients, it has been shown to provide an immediate reduction in pain not only at the site of needled-MTrP but also in areas affected by referred pain, which is normally followed by functional changes (Dommerholt, 2011; Dommerholt et al., 2019). Furthermore, increased use of MTrP-DN could help to reduce the need for analgesics and opioid prescriptions, particularly in emergencies (Dommerholt et al., 2019). These benefits of MTrP-DN, combined with the unfulfilled need of refractory MPS patients with persistent chronic pain, may have aided in its emergence as an acceptable treatment modality in MPS, at least in terms of geographic availability, practicing professional specialties, and third-party

authorizations for insurance coverage or reimbursement (Unverzagt, et al., 2015; Dommerholt et al., 2019;).

The expanding role of dry needling as a treatment approach is not limited to MPS; rather, it has been increasingly evaluated as a treatment modality in a variety of neuromusculoskeletal painful conditions manifesting with or without trigger points and involving neural and connective tissues at a variety of non-muscular anatomical regions, including tendons, scars, and entrapped nerves; MTrP-DN, however, remains one of the most commonly researched and utilized manifestations of dry needling (Dunning et al., 2014; Dommerholt, et al., 2019).

The clinical effectiveness of MTrP-DN in MPS has been evaluated both alone and in combination with many other treatment modalities. However, based on the substantial reported efficacy of multimodal approaches, it has been recommended to impart it as part of an individualized, comprehensive, and multimodal treatment program that includes both pharmacological and non-pharmacological interventions, such as the patient education on pain neuroscience, local and aerobic exercises, stress reduction, and overall functional rehabilitation (Fernández-de-Las-Peñas & Nijs, 2019).

MTrP-DN, like other types of manual therapy has been criticized for being a passive pain treatment solution that should be coupled with active, patient-led pain treatment approaches to achieve long-term functional rehabilitation wherever possible (Fernández-de-Las-Peñas & Nijs, 2019). Notably, aggravating factors must be kept to a minimum (Hong, 2006). MTrP-DN may be one of the most reliable and effective approaches to short-term pain relief in MPS. (Desai et al., 2013; Unverzagt et al., 2015). While the mechanisms involved in the role of MTrP-DN in MPS are not fully comprehended, they point to various actions at neural, muscular, and connective tissues surrounding the MTrPs, which result in a rapid and important reduction in the generation of peripheral nociceptive inputs, and also contributes to

peripheral, spinal, and supraspinal desensitization, as well as the activation of multiple central pain regulatory pathways and functional regeneration of neuro-myofascial tissues, reducing pain and improving quality of life in MPS patients (Vulfsons, et al., 2012; Dunning et al., 2014; Cerezo-Téllez, et al., 2018; Fernández-de-Las-Peñas & Nijs, 2019).

However, not all MPS patients can experience the same clinical benefits from MTrP-DN. For example, one study showed that patients with very long durations or high intensities of pain, as well as those who engage in repetitive work or have coexisting sleep deprivation, do not receive adequate short-term pain relief and continue to complain of pain after MTrP-DN (Huang et al., 2011). On the other hand, another research reported that the baseline perception of pain during the contraction of the concerned muscle was correlated with a successful clinical response (Koppenhaver et al., 2015). More data, however, is needed to explain the predictors of MTrP-DN in MPS.

Furthermore, some factors that should be evaluated in order to prevent complications include needle phobia, anticoagulant use and bleeding tendencies, conditions of poor general health, including frailty, immune deficiencies, including diabetes, pregnancy, conditions of poor mental health, epilepsy, and anatomical proximity to key vessels, nerves, or other sensitive zones, could preclude the patient from receiving MTrP-DN (Unverzagt et al, 2015).

3.10 Concepts and History of Dry Needling

The concept of dry needling originated in the 1940s, following the publication of Kelly's findings about the related effectiveness of injections of anesthetics and normal saline in the treatment of myofascial pain (Travell & Simons, 1983). Steinbrocker hypothesized in 1944 that needling alone without an injectate had a clinical effect and he observed a localized twitch response upon needle insertion and termed it "injection effect," which Travell then observed again in 1968, which then coined the word "dry needling (Bennet, 2007). The first major demonstration of its clinically significant impact in MPS has been accredited to Lewit, who registered a case series of 241 patients in 1979 inspired by Travell's MTrPs injection techniques – needling without an injectate using hollow needles – and named this the "needle effect" (Lewit, 1979; Shah et al., 2015).

Several realistic models of dry needling have been illustrated over the last few decades. The superficial dry needling model, which is considered a more static approach and was publicized by Baldry; and the deep dry needling or trigger point model, which is regarded as a more dynamic approach and was publicized by Travell and colleagues, which remains the most studied and practiced model of MTrP-DN (Travell & Simons, 1983). The superficial and deep MTrP-DN have also been reported to function through diverse and distinct mechanisms, which may be differentiated by their main sites of action, i.e., only at the level of nociceptive spinal afferents versus those at the additional levels of motor and autonomic spinal efferents, as well as spinal afferents, respectively (Kaljić et al., 2018). However, another suggested dry needling model employs electrotherapy, which was publicized by Gunn and was also known as the radiculopathy or neuropathy model, which may have some similarities with electroacupuncture (Unverzagt et al., 2015). Fischer's model is another model that involves dry needling and infiltration anesthesia and is based on spinal segmental sensitization (Fischer, 1997).

Although MTrP-DN has evolved independently over the last couple of decades and is based on modern anatomical and physiological concepts, it still shares some similarities with acupuncture, an ancient Chinese medicine treatment modality such as the insertion of solid fine needles onto specific selected points (Fernández-de-Las-Peñas, 2019). Traditional Chinese Medicine concepts describe the needling of Ah Shi acupoints, local tender spots of pain that overlap with known trigger points (Shah et al., 2015). According to Melzack, "trigger points and acupuncture points for pain [i.e. Ah Shi points], though discovered independently, and labeled differently, represent the same phenomenon and can be explained in terms of the same neural mechanisms (Melzack, 1977). The discussion of whether MTrP-DN is considered a form of acupuncture is an ongoing debate in pain management (Unverzagt et al., 2015).

Currently, MTrP-DN is typically performed sequentially for the main (primary) active trigger points, which can also inactivate the secondary (satellite) MTrPs located in the area of referred pain; however, some studies indicate that MTrP-DN on even latent MTrPs can help avoid the emergence of active MTrPs in the involved muscles (Hong 2006; Hsieh et al., 2007). Furthermore, one research concluded that MTrP-DN in the forearm muscles could minimize the excitability of MTrPs in the neck muscles (Tsai et al., 2010). Comparably, another report discovered that MTrP-DN in the shoulder muscles could reduce the mechano-sensitivity of the forearm muscles (Calvo-Lobo et al., 2017). As a result, dry needling may have a broader function in deactivating the primary, secondary, and remote (segmental) MTrPs. Also, further studies are needed to evaluate if there are any clinically significant centrally mediated effects of the MTrP-DN on the non-segmental MTrPs.

However, a point of contention in the MTrP-DN trigger point model is the clinical significance of eliciting a sustained local twitch response during the intervention by using fast needling maneuvers to reach the multiple sensitive loci (nociceptors) within the MTrP. This motor response has been suggested to break the MTrP circuit by producing vasodilation and

reducing the motor endplate noise and neurotransmitters associated with the MTrP (Hong, 2006; Fernández-de-Las-Peñas & Nijs, 2019; Shah et al., 2015). On the other hand, it has been proposed that deliberately re-eliciting the local twitch responses does not result in significant additional benefits in clinical outcomes but may instead increase the muscle soreness associated with the procedure (Perreaul et al., 2017).

MTrP-DN is now usually done with single-use, sterile, thin (less than 1 mm in diameter), filiform (solid) needles. According to one study, triple-polished and triple-lubricated needles with smooth and sharp tips may be recommended over oiled needles with blunt tips because they are easier to handle and may suffer less damage during deep MTrP-DN (Poveda-Pagán et al., 2018). Another research compared the effectiveness of MTrP-DN with different needle diameters of 0.35 mm, 0.5 mm, and 0.9 mm, and found similar analgesic effects for all three. A needle with a smaller diameter can cause less tissue damage, decreased needling pain, and higher acceptance for retreatment, while a needle with a larger diameter can result in better accuracy, particularly in regions with thicker tissues, and higher long-term effectiveness, though it may inflict more needling pain and may reduce the desire for retreatment (Wang et al., 2016).

3.11 Dry Needling Stimulates Neural, Muscular, and Connective Tissues

Although the mechanisms underlying MTrP-DN are only partly understood, the technique can effectively minimize myofascial pain through direct removal of nociceptors in the MTrPs and multiple complementary peripheral, spinal, and supraspinal neural mechanisms, so it is regarded as a neuro-myofascial stimulation technique; moreover, MTrP-DN can facilitate the healing and regeneration of the affected myofascial tissues through a variety of mechanisms, resulting in improved overall function after MTrP-DN (Dommerholt et al., 2006;

Cagnie et al., 2013; Fernández-de-las-Peñas & Dommerholt, 2013; Dunning et al., 2014). Some other authors, including some physical therapy boards, interpret MTrP-DN with a limited view of intramuscular stimulation and regard it as a myofascial (non-neural) stimulation technique (Dunning et al., 2014).

However, most of the studies have only examined the effects of MTrP-DN in bits and pieces. Few studies have illustrated that MTrP-DN has effects on neural, muscular, and connective tissues simultaneously, with the neurophysiological mechanisms receiving the most scientific attention. The fascial processes, by comparison, are the least accepted and are probably much less known than the others.

Another limitation of DN study is the combination of MTrP-DN and acupuncture. While the impacts of acupoint needling when undergoing acupuncture may be similar and have, therefore, been included in literature reviews on MPD and MTrP-DN, it would also be ideal for reproducing those observations in MTrP-DN studies. Nonetheless, despite rational professional limits, the comprehensive literature on demonstration of peripheral and central desensitization with acupuncture-related dry needling cannot be ignored and may be highly applicable to MTrP-DN (Dunning et al., 2014; Perreault et al., 2016; Fernández-de-Las-Peñas & Nijs, 2019).

A large number of underlying peripheral and central mechanisms, including chemical, mechanical, and hormonal mechanisms, have been proposed for the effects of MTrP-DN on peripheral, spinal, and supraspinal neural tissues, in addition to blocking nociceptive signaling and activating several classes of spinal afferents; furthermore, MTrP-DN affects endogenous opioids and cortical pain processing (Cagnie et al., 2013; Fernández-de-las-Peñas & Dommerholt, 2013; Dunning et al., 2014; Perreault et al., 2016; Fernández-de-Las-Peñas & Nijs, 2019). Based on acupuncture studies, the descending pain pathway has also been proposed to play a significant role in MTrP-DN-related analgesia (Chou et al., 2012).

Intriguingly, it has recently been demonstrated that MTrP-DN in MPS patients decreases neuromuscular junction irritability (motor endplate noise) and sympathetic hyperactivity in the affected areas, which can potentially minimize the overlap of contractile proteins and relax the sarcomeres (Ozden et al., 2016; Fernández-de-Las-Peñas & Nijs, 2019). Furthermore, another recent research found that MTrP-DN reduced muscle stiffness and mechanical heterogeneity on ultrasound elastography, which is consistent with older hypotheses of MTrP-DN-induced contraction knot disruption and facilitation of muscle regeneration (Dommerholt et al., 2006). Improvements in blood flow to the muscle tissues on MTrP-DN have also been documented (Cagnie et al., 2013).

Additionally, it has been proposed that MTrP-DN restricted to connective tissues, specifically the rotation of the needle within the fascia, can induce mechano-transduction, resulting in stimulation of mechanoreceptors and nociceptors as well as changes in the extracellular matrix composition and the concentration of vasoactive molecules and neurotransmitters (Dommerholt et al., 2006; Kaljić et al., 2018).

3.12 Dry Needling Compared to Sham or Control

Although truly blinded and sham-controlled trials for MTrP-DN are difficult to design, several clinical trials with a reasonable amount of blinding and sham treatment have been recorded, with the majority revealing its clinical efficacy and a minority revealing no additional benefits of MTrP-DN (Dommerholt, 2011; Tekin et al., 2013). Nonetheless, legitimate concerns have been raised about the need for improved clinical trial design and the use of sham therapies that are as similar to the MTrP-DN as possible (Kietrys et al., 2013; Gattie et al., 2017).

Importantly, a more recent phenomenon that has improved the clinical utility of the evidence from those trials is the collection of their data in the form of well-designed systematic reviews and meta-analysis, which can provide clinically relevant conclusions about the efficacy of MTrP-DN versus sham or placebo across various body regions that are primarily involved in MPS (Kietrys et al., 2013; Liu et al., 2015; Rodríguez-Mansilla et al., 2016; Espejo-Antúnez, et al., 2017; Gattie et al., 2017; Hu et al., 2018; Navarro-Santana et al., 2020; Navarro-Santana et al., 2021;).

Most of the recommendations in most of these systematic reviews were deemed to be validated by low-to-moderate quality evidence at best, and much emphasis was placed on MPS affecting the neck and shoulder regions. However, almost all reviews have acknowledged the added therapeutic benefits of MTrP-DN over sham/placebo on pain intensity, although evidence on the benefits relayed to functional improvements is mixed. Importantly, the evidence for the greatest magnitude of benefits with MTrP-DN pertains to the immediate or post-intervention duration, which may last for at least a few weeks, and many of the reviews have identified the unfulfilled need for documenting long-term outcomes of MTrP-DN.

Table 2 summarizes the outcomes of recent systematic reviews comparing MTrP-DN versus sham or control.

Table 2. Key Findings of Recent Systematic Reviews on Effectiveness of Dry Needling versus Sham or Control in Myofascial Pain Syndrome

Body Region(s)	**Comparative Findings of Systematic Review Against Sham or Control**	**Author(s), Year**
Neck, shoulder, and upper back [upper quarter muscles]	- Grade A (Level 1a) evidence for the effectiveness of MTrP-DN.	Kietrys et al., 2013

	- Recommended MTrP-DN compared to sham/placebo for immediate, and 4-week pain relief.	
Neck and shoulder	- Short- and medium-term effectiveness of MTrP-DN versus sham/control.	Liu et al., 2015
Any site	- MTrP-DN was inferior to placebo/sham in terms of pain relief. - MTrP-DN was superior to placebo/sham in terms of range of motion improvement.	Rodríguez-Mansilla et al., 2016
Neck and shoulder	- Compared to sham/placebo/no intervention, MTrP-DN more effective at reducing short-term pain, and improving range of motion and quality of life.	Espejo-Antúnez, et al., 2017
Any site	- Low to moderate-quality evidence indicates that MTrP-DN improves short-term pain and function more effectively than that by sham/placebo. - Evidence lacking for long-term benefits.	Gattie, Cleland & Snodgrass, 2017
Low back	- MTrP-DN is superior to sham post-intervention and on follow-up in terms of pain relief. - MTrP-DN is superior to sham post-intervention but not on follow-up in terms of functional improvement.	Hu et al., 2018

Neck	- Low to moderate-quality evidence indicates short-term effectiveness of MTrP-DN in reductions of pain intensity and pain-related disability but did not indicate range of motion improvement.	Navarro-Santana et al., 2020
Shoulder	- Short-term pain intensity reduction with MTrP-DN.	Navarro-Santana et al., 2021

3.13 Dry Needling Compared to Other Treatments (Laser and Trigger Point Injections)

Although trigger point anesthetic injections have long been used in MPS, only a few head-to-head clinical trials have compared MTrP-DN to wet needling, with mixed results. In one such study, both MTrP-DN and wet needling were found to be equally efficient in pain relief when followed by a local twitch response, but MTrP-DN had a substantially higher prevalence of post-injection pain (Hong, 1994). Another trial found a higher prevalence of post-injection soreness with MTrP-DN, as well as higher patient satisfaction with wet needling (Ibrahim & Abdelrahem, 2019). In contrast, another trial found that MTrP-DN and wet needling were equally effective in MPS (Eroğlu et al., 2013).

An analysis of the cumulative evidence for the comparative efficacy of MTrP-DN and trigger point anesthetic injections yields conflicting results. A meta-analysis of their comparative efficacy in the upper quarter muscles and another in the neck and shoulder regions revealed that lignocaine injections were more efficient in the short and mid-term pain relief, respectively (Kietrys et al., 2013; Liu et al., 2015). Conversely, another meta-analysis

involving the head and neck regions reported no variation in the efficacies of the two therapies (Ong & Claydon, 2014). Also, a systematic review found no difference between the two treatments; they even suggested that the needling effect could be responsible for the efficacy even in the group receiving anesthetic injections (Cummings & White, 2001). Therefore, larger and better-designed head-to-head clinical trials are needed to draw definitive conclusions on the comparative efficacy of MTrP-DN and wet needling.

Laser therapy is a potential treatment for MPS because it is a non-invasive alternative for deactivating MTrPs and enhancing their microcirculation and biochemical milieu, which could benefit patients who are afraid of needles (Ilbuldu et al., 2004; Uemoto et al., 2013). According to one study, laser therapy to MTrPs but not acupoints improved short-term pain and function in MPS patients (Chang et al., 2020).

In multiple trials involving the Trapezius muscle, low-level laser therapy has been tested for comparative efficacy against MTrP-DN, which tend to have limitations similar to other trials involving dry needling, showing conflicting findings. In one study, low-level laser administration over the MTrPs was found to be more efficient than MTrP-DN post-treatment (Ilbuldu et al., 2004). Similarly, in another trial, the variations were found to be non-significant, but in favor of low-level laser therapy (Agung et al. 2018). Another trial showed MTrP-DN as a more effective option than low-level laser therapy (Seifolahi et al., 2021).

A recent trial compared the combination treatment of MTrP-DN and low-level laser therapy to MTrP-DN alone in MPS involving the trapezius muscle (Motavalian et al., 2020). The trial found that the combination therapy improved short-term pain and function more than MTrP-DN alone. Another recent study, which did not involve MTrP-DN, investigated polarized low-level laser therapy in MPS and discovered that it was more efficient than low-level laser therapy, which could influence future trials (Shahimoridi et al., 2020).

According to recent systematic reviews, MTrP-DN is as efficient as physical therapy, including manual therapy and kinesiotherapy, in the short-term improvement of pain and function. However, the combination of MTrP-DN with manual therapy or kinesiotherapy is more effective than any of these therapy approaches when used independently (Lew et al., 2020; Fernández-De-Las-Peñas et al., 2021).

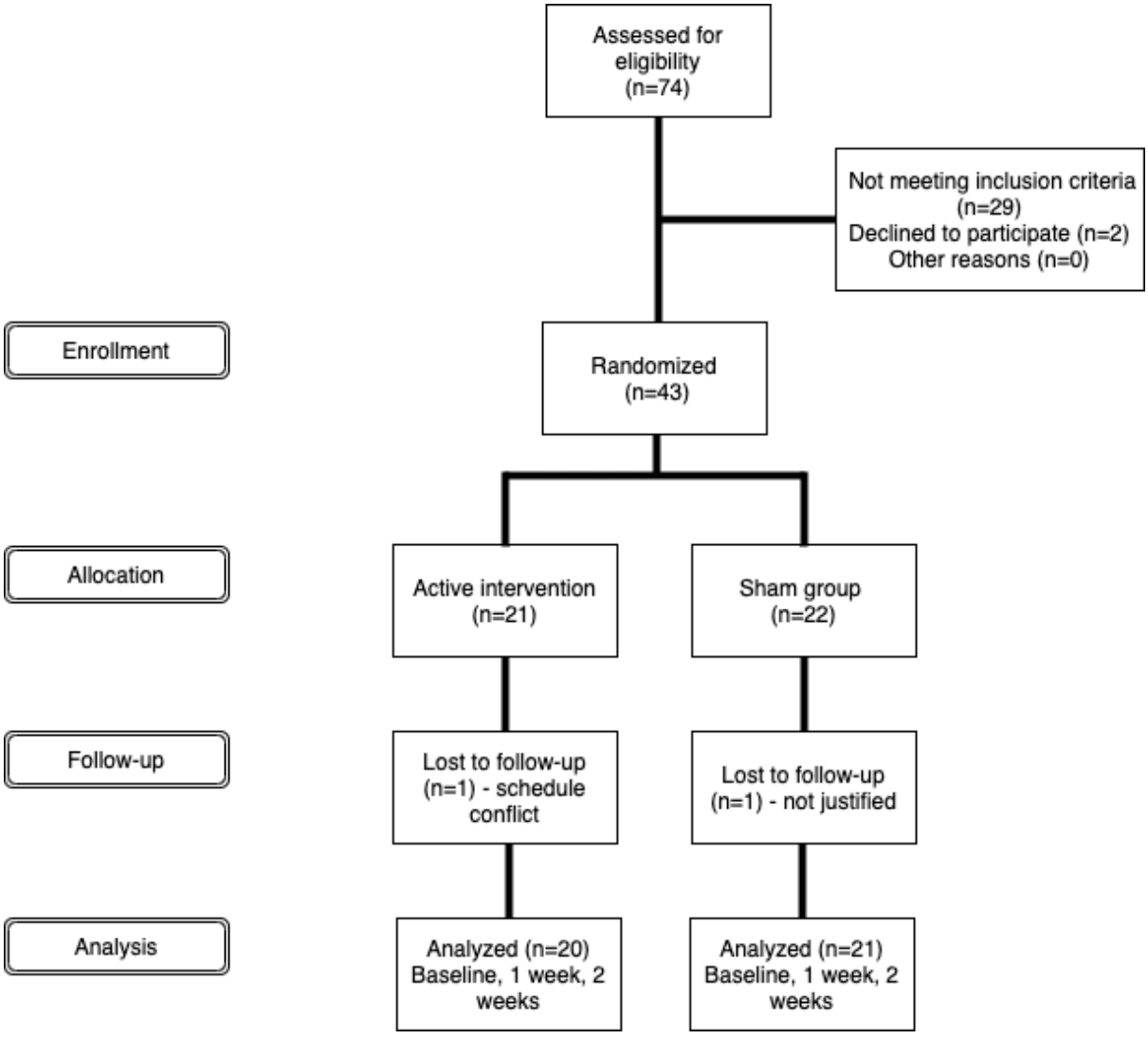
4 METHODS

4. METHODS

4.1 Study design

This study was designed as a two-parallel arm, randomized, and sham-controlled trial, with an allocation ratio of 1:1. The study was approved by our Institution's Ethics Review Board (# 0447/10), and all patients provided written informed consent before inclusion in the study. The trial was registered at Clinical Trials (#NCT02179320). Participant enrollment is presented in Figure 1. A total of 74 patients were screened for participation, 43 patients were randomized, 21 for the active and 22 for the sham group.

Figure 1. Participant flow diagram.



4.2 Patients

Consecutive patients were recruited in several pain clinics in the area of São Paulo, Brazil, and assessed at the Pain Center of the Hospital das Clinicas of the University of Sao Paulo, Brazil. All patients had chronic nociceptive shoulder pain where myofascial pain syndrome (Dommerholt & Fernández-de-las-Peñas, 2013) was considered to be present and constituted a major cause of pain according to the assessment of two independent physiatrists (MBP, JTT). Inclusion criteria included individuals aged 18-70 years, presence of chronic unilateral shoulder pain or asymmetrical bilateral shoulder pain, with the most painful side presenting a score of at least 40/100mm higher in the visual analogue scale (VAS, ranging from 0: no pain to 100: maximal pain imaginable) compared to the less painful shoulder. Other inclusion criteria included the presence of non-traumatic chronic shoulder pain due to at least one of the trapezius muscle trigger points (Cagnie et al., 2012), pain duration longer than 3 months (>15 days per month with pain). Concomitant medication for pain and sleep disorders was allowed, provided that their doses were stable for at least 30 days before enrollment and remained unchanged during the study. Patients were not included if evidence of neuropathic pain was present (i.e., a positive *douleur neuropatique*-4), if they had intermittent pain patterns (<15 days per month), if they refused to provide consent for participation, or if they had evidence of another painful shoulder disorder such as subacromial impingement syndrome, adhesive capsulitis, calcific tendonitis of the rotator cuff and severe rotator cuff tendon alterations. All patients underwent shoulder radiography and, in some instances, ultrasound exams to exclude major structural disorders. Patients with known fibromyalgia or rheumatic diseases were excluded (Borg-Stein & Simons, 2002; Wolfe et al., 2016). Patients with a current primary psychiatric condition, including major depression or major personality

disorders according to *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria, a history of drug or alcohol abuse based on the CAGE (Mayfield et al., 1974) questionnaire were excluded. Patients were also excluded if they were to be enrolled in another clinical trial during the study or if they had participated in a clinical trial within the previous 6 months before enrollment.

4.3 Experimental design

Randomization was performed via the website *www.randomizer.org*. Patients were matched according to age and sex in blocks of six. The active needling group (A) was composed of participants who underwent one session of standardized trigger-point dry needling, and by the sham group (S) receiving a standardized sham session of dry-needling (Schulz et al., 2010).

Patients were assessed in three face-to-face visits: D0: one week before needling, D7: day of needling, and D14: one-week post-needling follow-up:

D0 – at enrollment, patients were assessed for eligibility. If enrolled, they were instructed to fill in a 14-day pain diary in which the worst, average, and lowest daily pain intensities were recorded, using the self-rating eleven-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain) from the brief pain inventory (Cleeland & Ryan, 1994; Ferreira et al., 2011), in order to establish a baseline pain level before the needling. Patients were also instructed to record any adverse events of the therapy during the study period.

D7 - Patients were randomly assigned into two treatment arms (active or sham treatment). They filled in a pre-procedure pain and mood assessment battery. QST was performed at three sites before and right after the needling procedure at the: i. skin area over

the painful trapezium, ii. the contralateral mirror area, and iii. a control area on the trunk (dermatomes T6-8) over of the rib cage, at a site with no local or referred pain) (Table 3, which demonstrates experimental study outline design)

D14 – A third QST battery was performed, and the same pain and mood assessment from baseline were filled in.

Table 3. Study design

Visit	Screening	Baseline (D0)	D7	D14
Inclusion / Exclusion criteria	X			
Consent form	X			
MQS	X	X	X	X
Clinical scales				
DN4	X			
NRS	X	X	X	X
Trigger point Evaluation	X	X	X	x
Pain diary		X	X	X
BPI			X	X
McGill			X	X
HAD			X	X
CGI				X
Sensorial testing				
QST			X	X

Legend: Experimental study outline design. Each subject was evaluated on 3 days (D0, D7 and D14). Treatment was performed on D7. QST was performed before and after treatment on D7, and on D14. Pain questionnaires were performed on D7 and D14.MQS = Medication quantification scale, DN4 = Douleur neuropatique 4, NRS= Numeric rating scale, BPI = Brief pain inventory, McGill = McGill short form pain questionnaire, HAD = Hospital anxiety and depression scale, CGI = Clinical global impression scale, QST = Quantitative sensory testing

4.4 Description of needling procedure

Patients were blinded to which treatment they received. Patients underwent either an active or sham trigger point dry needling to the most painful trapezius muscle. The trigger point was previously localized by firm digital pressure through palpation of the trapezius muscle and pressure algometers with a 3 cm^2 hard foam tip to provide blunt-ended pressure of at least 2 kg/cm^2 (Wagner Instruments, USA). The identification was based on the operational definition of MTrPs by locating the presence of a palpable taut band and its hypersensitive area and a local pain response due to the palpation of the taut band or reproduction of referred pain (defined as 80% resemblance) in response to local digital compression (Travell & Simons, 1983). Patients were seated facing a research assistant, with minimal interpersonal interaction, and needling was performed by a specialist facing the patients' back. The researcher performing the needling procedure had no other role in the study or contact with patients except for the few seconds of the needling procedure duration. Each patient was treated only once. The pain specialist who performed the procedures had to certify that both treatments had the same 20-second duration and were similar in the intensity of trans-procedural pain elicited, which was controlled by the measurement of pain intensity on a VAS (0-no pain, 100mm- maximum pain imaginable) every 5 seconds during needling using a chronometer. The patients were asked to use the hand contralateral to the painful trapezius under treatment to score the VAS. The trigger point inactivation on the active group was performed according to the technique standardized by Simons *et al*., with 0.25 x 40mm Huanqiu® acupuncture needles. Patients who underwent sham treatment had the needle inserted intradermally, superficially, parallel to the skin, without reaching the muscle and its trigger point. The sham needling technique included twisting the needle in a plane parallel to the fascia so that some pain could be elicited from the procedure, but without having the needle inserted into the muscle's trigger point (i.e., the putative mechanism of action of active needling).

4.5 Main clinical endpoints

The primary outcome was pain intensity: average pain intensity over the last 24 hours, measured with an eleven-point numerical rating scale – NRS (0 = no pain, 10 = maximum pain imaginable) seven days after the procedure (D14). Baseline average pain intensity was assessed with the average pain of the 7 days prior to needling (from day 1 until 7 = baseline), on the day of the procedure (D7, before dry needling), and daily on the remaining 7 days (until day 14).

The secondary aim was to assess whether the analgesia due to dry needling correlated with acute DN-related alterations in mechanical hyperalgesia area and other sensory variables, such as cold-induced pain, mechanical hyperalgesia, or mechanical hyperesthesia.

4.6 Outcome measurements

- The visual analogue scale (VAS) is a self-report pain scale, consisting of a horizontal line of 100 mm in length, that is anchored by the ratings "no pain" at the left side (score 0) and "worst pain imaginable" at the right side (score 100) (Collins et al., 1997).
- The numerical rating scale (NRS) is a self-rating subjective pain measuring scale that measures pain from 0 (no pain) to 10 (worst pain) (Farrar et al., 2001).
- The *Douleur Neuropatique* 4 (DN4) questionnaire used for the screening of neuropathic pain (Bouhassira et al., 2005; Santos et al., 2010).
- The brief pain inventory (BPI) allows patients to rate the intensity of their pain and pain interference with daily activities (Cleeland & Ryan, 1994; Ferreira et al., 2011).
- The short-form McGill pain questionnaire (SF-MPQ) consists of 15 descriptors, which evaluate sensory, affective, and cognitive aspects of pain (Ferreira, 2011).

- The medication quantification scale, an instrument to quantify medication resgimen use in chronic pain populations (Harden, 2005)
- The hospital anxiety and depression Scale (HADS), a self-assessment scale, was used to evaluate the treatment effects on mood and anxiety (Zigmond & Snaith, 1983).

The global impressions of change consist of a Likert scale with seven points ranging from "very much improved" to "very much worse" based on the degree perception of change after treatment experience by the patient and the rater (clinician) (Farrar et al., 2001). Patients were classified as "improved" or "not improved" with improvement being a significant or moderate improvement and "not improved" being any other score.

4.7 Quantitative sensory testing

All participants underwent a QST battery over the painful referred pain are on the shoulder, a contralateral mirror area, and an area located ipsilateral to the pain side, over the T6-7 dermatomes over the flank. QST changes were compared between sessions at the painful side.

The QST battery assessed large fiber (Aβ) and small (Aδ and C) mediated somatic sensory inputs, assessed at three time-points: before DN, immediately after DN, and on D14 (7 days after the procedure).

Evaluation of mechanical static tactile sensitivity was performed with calibrated Von Frey monofilaments ranging from 0.008 to 300g (manufactured by Somedic, Sweden – Senselab Aesthesiometer), of increasing thicknesses, for determining the threshold of tactile and pain detection, exerting greater pressure on the skin as the monofilament caliber increased. The detection of pain thresholds, supraliminal stimulations with strands two and three times

thicker than the ones used for determining pain threshold were made so that mechanical hyperalgesia was evaluated through the visual analogue scale after each stimulus.

Finally, the mechanical hyperalgesia area (cm^2) boundaries were determined with suitable Von Frey filaments (Ranoux et al., 2008) and marked using a proper non-toxic pen. This area was then copied through transparent paper, scanned, and digitally quantified in the computer with Adobe Photoshop® CS4 11.0. For thermal non-painful perception and cold hyperalgesia, a custom-made contact thermode (USP, 2016) was applied over the painful trapezius muscle at two constant fixed temperatures of 15^o and 5^oC for 5 seconds.

4.7 Safety

The safety of dry needling was assessed by monitoring the occurrence of adverse effects during treatment by a dedicated recording file.

4.8 Blinding assessment

The blinding assessment was evaluated with a 4-question form, which asked patients whether they knew which group they were, which intervention they received, their pain intensity during needling, and if they would accept receiving the same treatment again if proposed and their justification (Rocha Rde et al., 2014).

4.9 Statistical analyses

Statistical analyses were conducted with SPSS version 22 (SPSS Inc, Chicago, IL). The categorical data were expressed in proportions, and continuous variables were expressed in

mean and standard deviation. The exploratory analysis initially evaluated distributions, frequencies, and percentages for each of the numeric and categorical variables. We assessed randomization effectiveness by evaluating balance regarding baseline variables, comparing the interventional and the control arms. The normality of the data was accessed by the Kolmogorov-Smirnoff test. In all cases, P values < 0.05 were considered significant.

The repeated measures ANOVA test was used for the comparison of the outcomes between the groups along the trial, including an interaction term between group and time and post-hoc analyses when indicated.

Correlation analyses between the main outcome results were performed to verify the association between pain improvement and quantitative sensory testing parameters. Only correlations with coefficients above 0.4 were reported. Since the Kolmogorov–Smirnov test revealed that secondary outcomes such as quality of life and QST values did not have a normal distribution, the differences between groups were compared using a non-parametric test (Kruskal-Wallis test, followed by pairwise comparisons of change between groups (Wilcoxon/s/Mann-Whitney's-U test). Bonferroni correction for multiple comparisons was used in these settings.

The sample size was calculated based on the effect size achieved by a previous trial (Tsai et al., 2010), considering a repeated-measures ANOVA approach and using the software G*Power 3.1.9.2 for Windows (California, USA). Bearing in mind the assumptions of an effect size of 0.4 (equivalent to an eta-squared effect size of 0.140), two-tailed α error level probability of 0.05, and a minimum power of 0.80, the estimated sample size needed would be 20 subjects per arm. We included three extra participants to account for loss of follow-up. Cohen's d, defined as the difference between the means of the 2 groups divided by the pool standard error, was used for the calculation of effect sizes.

5 RESULTS

5. RESULTS

5.1 Patients

Participant enrollment is presented in Figure 1. A total of 74 patients were screened for participation, 43 patients were randomized, 21 for the active and 22 for the sham group. Two patients were lost during follow-up, one from each group. The reasons for dropping out were specified in Figure 1. Table 4 shows the baseline characteristics of the trial participants. There were no significant differences between treatment groups regarding demographic and pain characteristics at baseline (all p values > 0.2). Patients included in this study had an average age of 58, and most were female (82%). All patients were trigger point dry-needling naïve.

Table 4. Demographics and baseline characteristics of patients.

Characteristics	**Active**	**Sham**	**p-value**
Age (years)	58.4 ± 14.5	58.2 ± 11.0	0.968
Sex, female n (%)	18 (90%)	16 (76%)	0.228
Pain intensity	6.3 ± 2.0	6.6 ± 1.7	0.651
DN4	2.4	2.4	
Concomitant treatment			
Regular analgesics n (%)	11 (55)	9 (42)	0.671
Antidepressants n (%)	3 (15)	3 (14)	0.343
Anticonvulsants n (%)	3 (15)	4 (19)	0.443

Legend: DN4: douleur neuropathique 4 questionnaire. * P<0.05.

5.2 Efficacy of dry needling on main outcomes

Dry needling had a significant effect on average pain intensity throughout the treatment, as shown by comparison with the sham group (Table 5; Figure 2). The group treated with active needling had significantly lower pain scores than the sham group at follow-up with an average pain intensity change from 6.30 ± 2.05 before the therapy to 2.40 ± 2.46 at the end of treatment (D14) in the active and 6.04 ± 1.32 before the treatment to 5.14 ± 1.49 at the end of therapy (D14) in the sham group, ($F(1,39)=5.908$; $p=0.02$; 95% CI, 1.25-3.55, Cohen's d effect size = 1.34 (Cohen, 1988).

Post-hoc analysis with adjustment for multiple testing revealed that NRS pain score was statistically significantly decreased from baseline to D14 [2.350 (95% CI, 1.781 to 2.919), $p < .001$]. There was also a statistically significant difference in NRS at D14 between groups, $F(1, 39) = 74.41$, $p = <0.01$, partial $\eta 2 = 0.317$. There was a statistically significant effect of time on NRS pain for the sham group, $F(1, 20) = 7.211$, $p < 0.014$, partial $\eta 2 = 0.265$. and for the active DN group, $F(1,19) = 55.682$, $p < 0.001$, partial $\eta 2 = 0.746$ (Table 6).

Table 5. Pain intensity scores for the two groups

		NRS (0-10)	
Variable	**Baseline**	**D14**	**P**
Sham	6.0 ± 1.32	5.1 ± 1.49	0.214
Active	6.3 ± 2.05	2.4 ± 2.45	0.040
P	0.246	<0.001	0.020[a]

Legend: The values are presented as mean ± standard deviation. NRS: numerical rating scale, BPI: brief pain inventory.[a] p value for the interaction term between group and time (0-10).

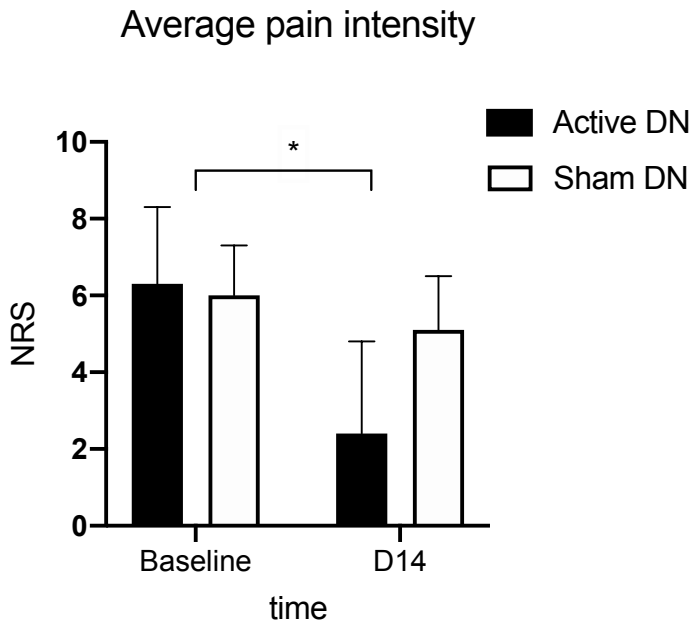
Table 6. Descriptive statistics of pain intensity at baseline and D14

Treatment	Time	Mean		95% Confidence Interval	
			Std. Error	Lower Bound	Upper Bound
Sham DN	Baseline	5.8	0.321	5.128	6.472
	D14	5.0	0.332	4.304	5.696
Active DN	Baseline	6.3	0.459	5.338	7.262
	D14	2.4	0.550	1.250	3.550

Legend: 95% Confidence Interval at D14. DN = dry needling.

Figure 2.

Mean changes in average pain intensity.



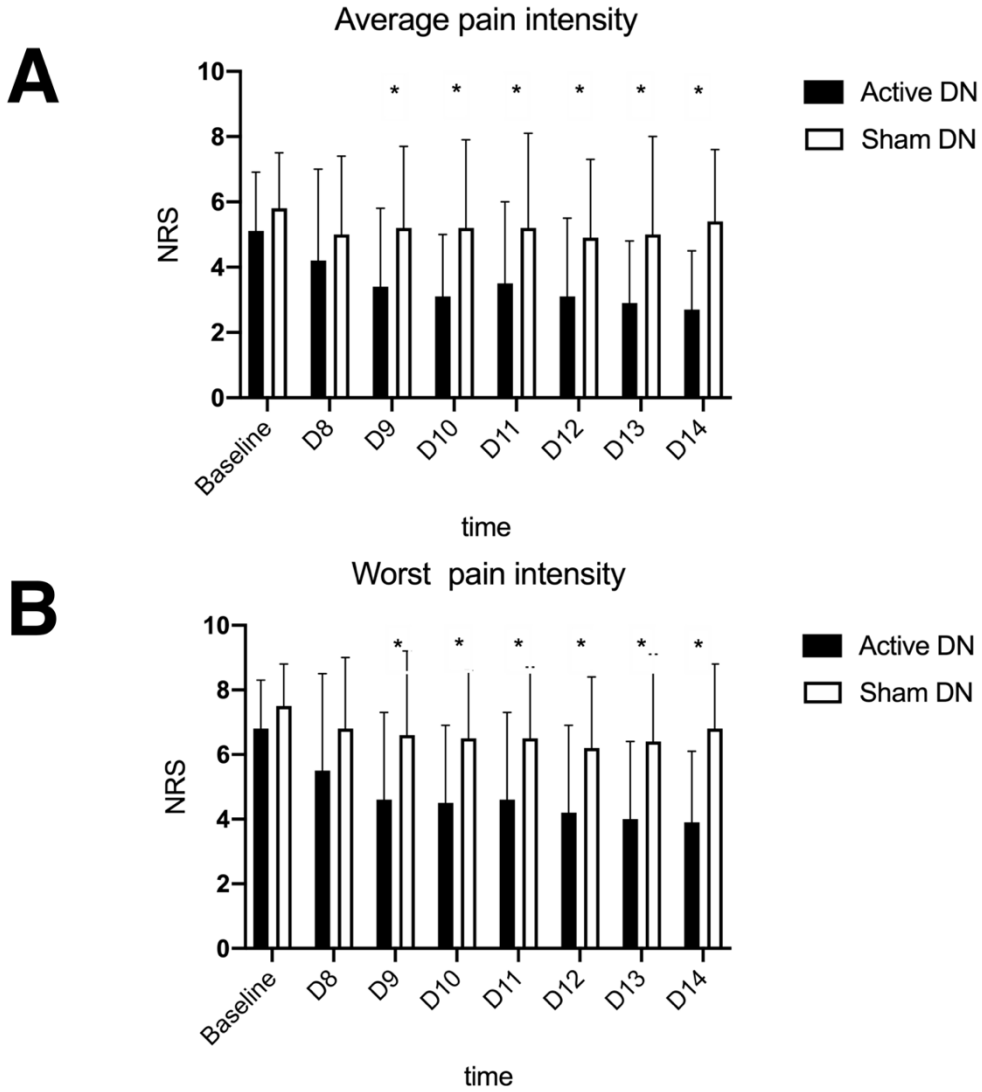
Legend: Error bars represent standard error of the mean (S.E.M.)

5.3 Efficacy of dry needling and its immediate effects on pain

One single session of dry needling resulted in significant pain reduction in the BPI-*worst* and BPI-*average pain* (Figure 3) score starting from D9 (2 days after needling) up until D14 (Table 7), suggesting a sustained persistent analgesic effect in the active group only during this period. There was a statistically significant interaction between the intervention and time on BPI-average pain reduction from D9 to D14, $F(7,273) = 3.047$, $p = 0.004$, 95% CI, 0.565 – 3.174, and BPI-worst pain reduction from D9 to D14, $F(7,273) = 2.959$, $P = 0.005$, 95% CI 0.591 – 3.223). We found no significant pain reduction for the weakest pain in any of the evaluated days.

Figure 3.

Changes in pain intensity for average and worst pain over time.



Legend: Error bars represent standard error of the mean (S.E.M.). *P<0.05

Table 7: Results of the effects of dry needling on pain

	Baseline	D8	D9	D10	D11	D12	D13	D14
BPI-worst pain Active	6.84 ± 1.58	5.50 ± 3.03	4.65 ± 2.71*	4.50 ± 2.46*	4.65 ± 2.73*	4.25 ± 2.76*	4.05 ± 2.41*	3.95 ± 2.25*
BPI-worst pain Sham	7.50 ± 1.33	6.80 ± 2.29	6.66 ± 2.61	6.57 ± 2.18	6.57 ± 2.29	6.23 ± 2.23	6.42 ± 2.71	6.85 ± 2.03
BPI-average pain Active	5.11 ± 1.81	4.20 ± 2.82	3.40 ± 2.43*	3.10 ± 1.99*	3.55 ± 2.52*	3.15 ± 2.43*	2.90 ± 1.97*	2.70 ± 1.89*
BPI-average pain Sham	5.84 ± 1.76	5.04 ± 2.41	5.23 ± 2.50	5.28 ± 2.72	5.23 ± 2.91	4.90 ± 2.46	5.04 ± 3.02	5.42 ± 2.22
BPI-lowest pain Active	3.75 ± 1.68	3.20 ± 2.70	2.60 ± 2.08	2.70 ± 1.89	2.65 ± 2.05	2.45 ± 2.18	2.30 ± 19.2	1.90 ± 1.74
BPI-lowest pain Sham	4.35 ± 2.11	4.09 ± 2.32	4.14 ± 2.43	4.00 ± 2.68	4.28 ± 2.41	4.04 ± 2.39	4.14 ± 2.63	5.42 ± 2.22

Legend: BPI: brief pain inventory. Values are presented as mean ± standard deviation.

*$p<0.05$

5.4 Effects of dry needling on pain secondary outcomes

Active dry needling significantly improved in the BPI-pain interference score, with patients reporting a marked decrease in the interference of pain with “general activities”, “mood”, and “sleep”, but no significant effect on “enjoyment of life”, “relationships” and “walk” compared to the sham procedure Dry needling had a significant effect on MPQ evaluative dimension of pain, but not on affective or sensory ones. Mean anxiety and depression scores measured on the HAD scale were not significantly affected by DN (Table 8).

5.5 Global impression of change

Patients in the active group reported 80.0% and 75.0% of “much improvement” in global impression of change – patient and clinician versions, respectively, compared with 33.3% and 42.9% for sham group (p=0.030 and p=0.037; respectively), the number necessary to treat = 2.1.

Table 8: Results of secondary assessments.

	Baseline (D0)		**Effect 1 week after needling (D14)**		**p-value**	**Effect size**
	Active	**Sham**	**Active**	**Sham**		
HAD depression	6.55 ± 4.65	7.71 ± 3.67	6.80 ± 3.92	7.66 ± 3.38	0.659	0.005
HAD anxiety	8.25 ± 3.76	10.1 ± 2.71	7.75 ± 3.02	9.61 ± 2.81	0.869	0.001
McGill VAS	6.30 ± 2.05*	6.57 ± 1.74	2.40 ± 2.45*	5.42 ± 1.71	**<0.001**	0.363

McGill sensory	4.40	±	4.66	±	3.90	±	5.00	±	0.226	0.037
	1.63		1.52		2.24		2.28			
McGill affective	3.25	±	3.57	±	2.55	±	2.85	±	0.979	0.0001
	1.55		1.24		1.76		1.52			
McGill evaluative	1.45	±	1.42	±	1.00	±	1.33	±	**0.110**	0.064
	0.51		0.50		0.64		0.65			
McGill 3 total dimensions	9.19	±	9.66	±	7.45	±	9.19	±	0.346	0.023
	3.84		2.26		4.37		3.84			
BPI %24h	40.75	±	45.23	±	60.00	±	45.23	±	0.160	0.050
	33.01		32.49		31.95		30.59			
BPI worst pain	7.25	±	7.57	±	4.15	±	6.28	±	**0.035**	0.110
	2.48		2.35		2.60		3.31			
BPI average pain	4.50	±	5.33	±	2.55	±	4.47	±	0.090	0.072
	2.13		2.37		2.25		3.09			
BPI lowest pain	2.65	±	3.80	±	1.95	±	3.14	±	0.948	0.000
	1.95		2.74		2.06		2.81			
BPI current pain	4.55	±	5.42	±	2.80	±	4.23	±	0.510	0.011
	2.81		3.29		2.74		2.89			
BPI general activities	5.50	±	4.95	±	2.20	±	4.66	±	**0.002**	0.229
	3.88		3.13		2.62		3.18			
BPI mood	4.80	±	4.61	±	2.80	±	4.38	±	**0.037**	0.107
	3.45		3.66		2.21		3.76			
BPI work	4.25	±	5.38	±	2.95	±	4.14	±	0.948	0.000
	3.55		4.21		2.87		3.67			
BPI relationships	1.40	±	2.38	±	1.50	±	2.80	±	0.746	0.003
	3.16		4.09		3.15		3.85			
BPI sleep	4.65	±	5.57	±	2.90	±	5.47	±	**0.020**	0.131
	3.51		3.10		3.29		3.58			
BPI enjoyment of life	2.30	±	4.42	±	1.45	±	4.28	±	0.526	0.010
	3.65		3.94		2.52		4.08			
BPI walk	0.65	±	1.85	±	0.55	±	1.57	±	0.868	0.001
	1.42		3.16		1.82		3.02			

BPI total interference (sum)	23.55 ± 14.37		29.19 ± 17.73		14.35 ± 11.93		27.33 ± 19.12		**0.037**	0.106

Legend: Comparison of the effects of dry needling or sham stimulation, from day 7 to day 14 on: the HAD depression and anxiety scores, the McGill questionnaire sensory, affective and evaluative scores, BPI total interference score, and its effect size. HAD: hospital and anxiety depression scale, BPI: brief pain inventory Data presented as mean ± standard deviation. P-value for the interaction between group and time.

5.6 Effects of dry needling on Quantitative Sensory Testing

DN produced a significant reduction in mechanical hyperalgesia on the skin over the painful area after needling [49.2 ± 37.4 cm^2 at baseline (D7), 39.2 ± 42.7 immediately after needling on D7; and 30.3 ± 28.5 cm^2 on D14, p = 0.001], for the active group when compared to sham stimulation. Other QST variables were not affected by treatment (Table 9).

Table 9. Quantitative sensory testing results of dry needling, before, immediately after, and 7 days after dry needling.

Variable	**Group**	**time**			**p value [a]**
		Before needling (D7)	**Immediately after needling (D7)**	**D14**	
Area of mechanical hyperalgesia (cm^2)	Active	49.2 ± 37.4	39.2 ± 42.7	30.3 ± 28.5	**0.001[a]**
	Sham	49.3 ± 33.4	44.5 ± 35.7	44.1 ± 34.8	
Mechanical detection threshold (g)	Active	3.0 ± 1.4	2.5 ± 0.7	2.5 ± 0.8	0.419
	Sham	2.7 ± 0.7	2.5 ± 0.7	2.7 ± 1.1	
	Active	19.1 ± 10.5	16.7 ± 7.9	15.9 ± 8.8	0.712

Mechanical pain threshold (g)	Sham	15.9 ± 10.4	15.3 ± 8.1	14.7 ± 7.1	
Mechanical hyperalgesia (VAS 0-100)	Active	30.4 ± 19.0	33.8 ± 25.7	25.0 ± 20.8	0.191
	Sham	28.8 ± 16.5	32.4 ± 20.2	32.1 ± 17.7	
Hyperalgesia (VAS 0-100)	Active	42.6 ± 26.1	39.9 ± 27.1	32.0 ± 24.2	0.200
	Sham	42.0 ± 22.0	42.8 ± 23.1	42.0 ± 18.7	
Cold hyperalgesia (VAS 0-100)	Active	17.9 ± 15.1	18.3 ± 21.6	15.2 ± 17.2	0.897
	Sham	19.4 ± 15.0	21.7 ± 16.9	17.1 ± 11.2	

Legend: VAS: visual analogue scale. Data is presented as mean ± standard deviation.[a] P value for the interaction term between group and time.

5.6 Medication use

Patients had an average MQS of 7.50 ± 3.18 in active, and 7.14 ± 3.19 in sham groups at baseline (p=0.67). At D14, MQS for the sham group was 6.85 ± 3.08 (p=0.55) and 7.10 ± 3.07 (p=0.57) in the active groups.

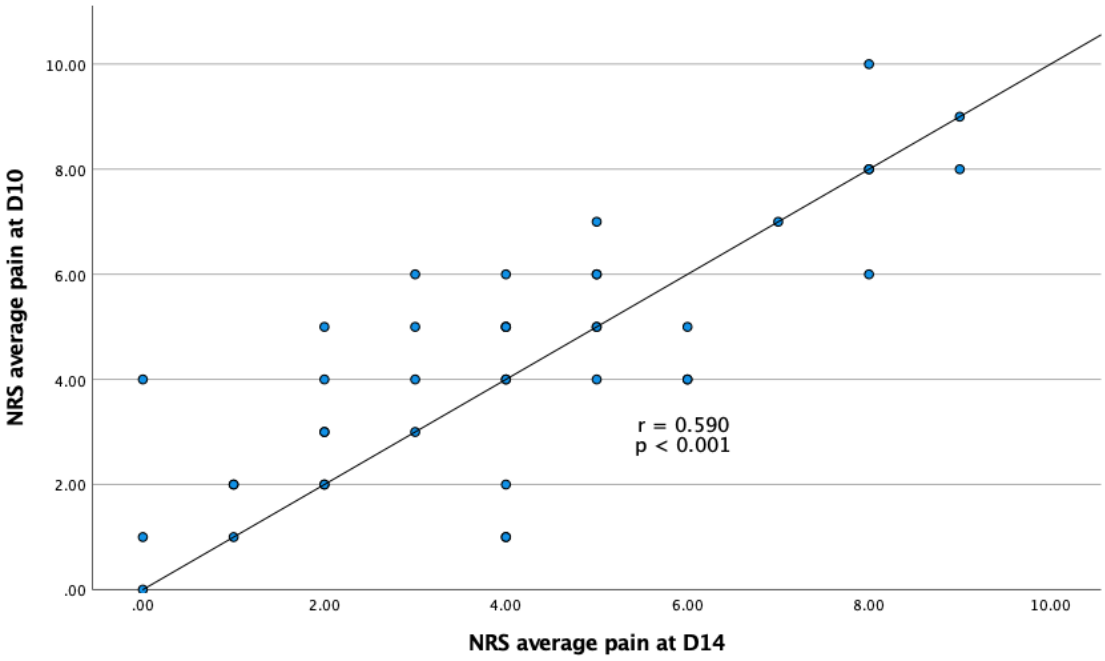
5.7 Correlation analyses

As expected, improvement of pain intensity was significantly correlated with an improvement on global impression of change both for patients and clinicians (rho=-0.630, p=0.003 and rho=-0.630, p=0.003, respectively). There was no correlation between BPI-average pain intensity improvement and changes on the area of mechanical hyperalgesia. Interestingly, we found a correlation between daily pain improvement starting 2 days (Figure 4) after active dry needling and a higher pain reduction during the following days until the last

assessment (D10: rho = 0.590, p = 0.013; D11: rho = 0.512, p=0.21; D12: rho = 0.772, p = 0.0001; D13: rho = 0.752, p = 0.0001; D14: rho = 0.670, p = 0.001).

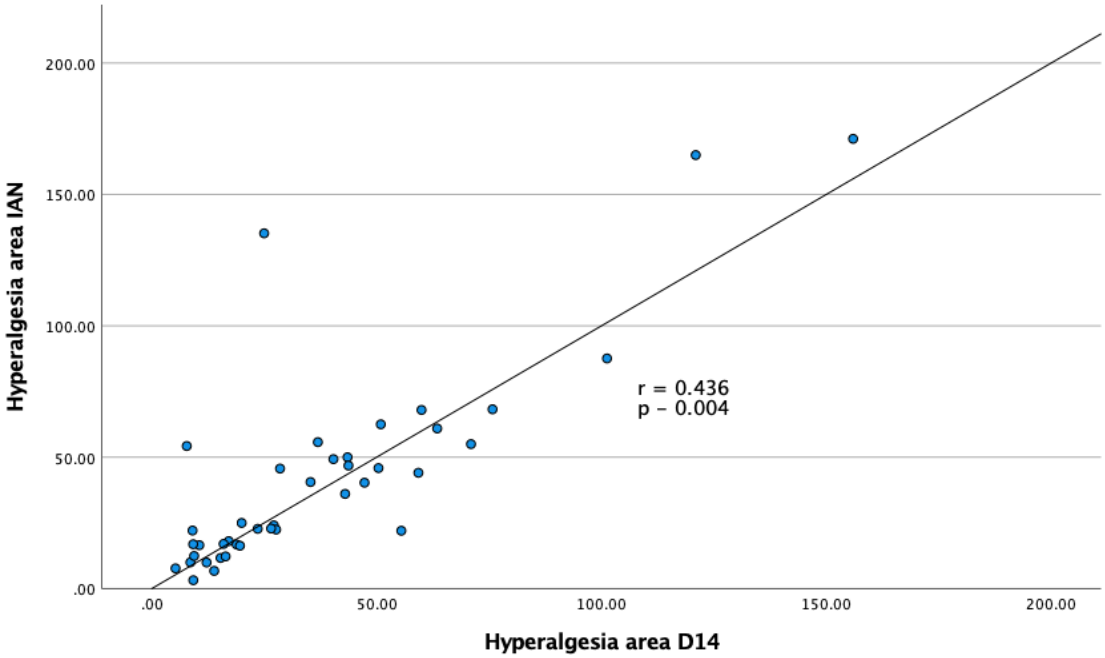
Also, patients who presented an immediate mechanical hyperalgesia area reduction after needling had a positive correlation with maintaining this positive area reduction response after 7 days on D14 (rho = 0.436, p = 0.004) (Figure 5). Additionally, patients who had a reduction of the area of mechanical hyperalgesia area had a positive correlation with decreasing mechanical pain threshold at D14 (rho = 0.413, p = 0.007) (Figure 6)

Figure 4. Scatterplot of NRS average pain at D10 versus NRS average pain at D14.



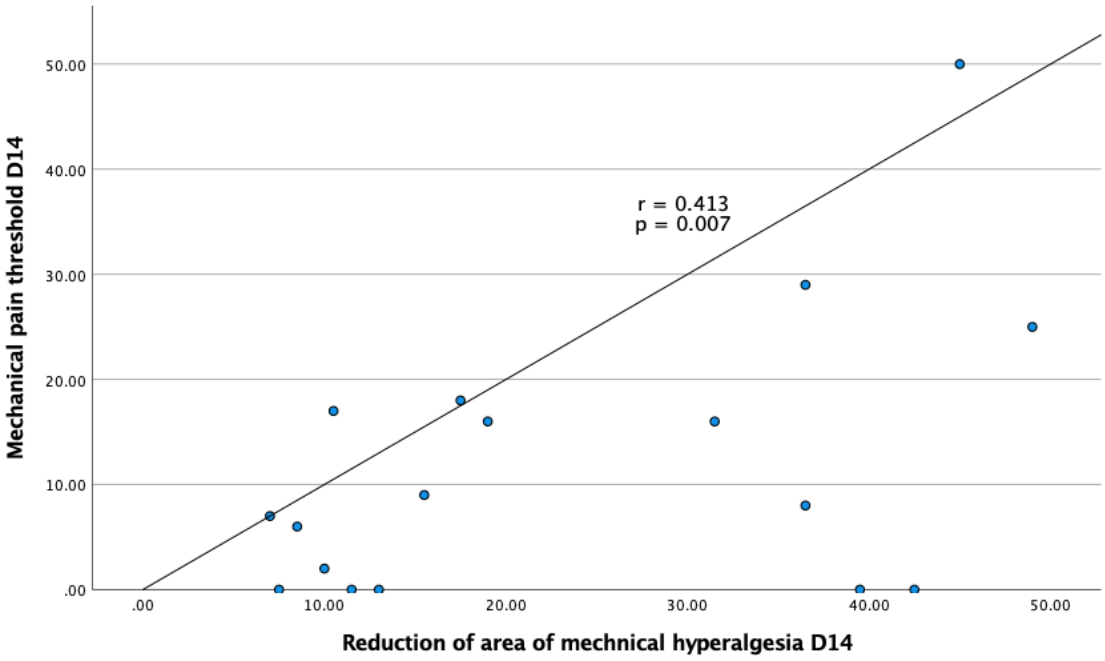
Legend: The regression line shows an average positive correlation (r = 0.590, p < 0.001), indicating that pain improvement in D9 is correlated with persistent pain improvement at D14.

Figure 5. Scatterplot of immediate mechanical hyperalgesia area reduction after needling (IAN) versus mechanical hyperalgesia at D14



Legend: The regression line shows an average positive correlation (r = 0.436, p = 0.004), indicating that immediate reduction after needling is correlated with maintenance of this positive area reduction response at D14.

Figure 6. Scatterplot of reduction of the area of mechanical hyperalgesia (cm^2) and correlation with decreasing mechanical pain threshold at D14



Legend: The regression line shows an average positive correlation ($r = 0.413$, $p = 0.007$), indicating that mechanical pain threshold improvement is correlated with reduction in area of mechanical hyperalgesia at D14.

5.8 Adverse Events

The dry needling treatment was well tolerated by patients. No major adverse events were reported from any patient included in this trial. Minor side effects such as minor local pain after dry needling were reported by 4 patients in the active group and 3 patients in the sham group, with no functional impact.

5.9 Blinding assessment

At the end of the study, 45% of the participants in the active group reported they were able to tell in which group they were allocated to, and among them, 55% guessed it right. In the sham group, these proportions were 62%, and 47%, respectively. When asked if the patients would like to maintain the sessions of active dry needling for a longer period, should this option be offered to them, affirmative answers were given by 70% of the active group, 55% of the placebo group. These proportions were not significantly different.

6 DISCUSSION

6. DISCUSSION

We have shown that chronic shoulder pain patients treated by dry needling had a significant improvement in pain intensity and pain interference with daily activities compared to sham procedure, an effect that persisted for at least 7 days. Improvements started two days after needling and persisted for at least 7 days thereafter. We have also described the temporal pattern of pain relief caused by DN, which started on the second and persisted until the seventh day post-procedure. The study also evaluated in a sham-controlled trial the effects of a single session of dry needling on pain intensity and explored the concomitant changes in cutaneous sensory thresholds with a battery of quantitative sensory testing (QST) in the painful (e.g., secondary hyperalgesia reduction), and its potential role in predicting the temporal persistence of the analgesic effects caused by the needle procedure.

DN analgesic effects were not limited to pain intensity, but also included positive effects of DN on pain interference with daily activities and improvement in global impressions of change. These are original information that add to a literature populated by studies devoid of sham arms (DiLorenzo et al., 2004; Bron et al., 2011; Gerber et al., 2015) or providing a superficial report on the sham technique (Diracoglu et al., 2012) such as its actual procedure, its duration, depth of needle insertion (Diracoglu et al., 2012) or pain intensity triggered by the sham procedure (Tsai et al., 2010; Chen et al., 2021). This last point is of significant importance since pain during sham needling may, by itself, engage nonspecific top-down pain modulatory systems and trigger pain relief that would be not specific and not related to the trigger-point treatment *per se*, being simply the fruit of the pain suppressive effect of a stronger concomitant nociceptive stimulus (Schliessbach et al., 2012). Here we took special care to control for the duration and for the intensity of both the active DN and its sham version, so that the effects of these biases would be mitigated.

Interestingly, the analgesic effects of dry needling were not immediate, as would have been expected in the case where its main mechanisms of action would uniquely lay on trigger point deactivation. Contrarily, our findings showed that a rather delayed response took place, commencing two days after the procedure, and with a positive correlation between daily pain improvement at this time-point and a more pronounced pain reduction at the seventh-day post-procedure. Many of the previous studies in the DN literature reported only immediate effects (Hong, 1994; Hsieh et al., 2007) of treatment, which have provided mechanistic insights into the technique in one hand, but limited clinical impact on the other. Additionally, this temporal profile of analgesia installation after DN may explain some negative results based on immediate pain assessment after the procedure (Huguenin et al., 2005). Considering these findings, we hypothesized that clinically meaningful pain improvement occurs after a delay of a few days after dry needling, and it may not be detected acutely. In this line, DN has previously been reported to possess analgesic effects for painful syndromes where myofascial pain was not present, suggesting that DN analgesic effects would rely not only on the mechanical effects of needle insertion and trigger point treatment, but, instead, on the engagement of other pain-suppressive mechanisms. For instance, a Cochrane systematic review of 35 RCTs evaluated the efficacy of dry needling and treatment of mechanical nonspecific low-back pain, with positive evidence of an immediate and short-term pain relief, although with a small effect size (Furlan et al., 2005). Similar findings have been reported for nonspecific shoulder pain (Calvo-Lobo et al., 2018) lateral epicondylitis-related pain (Uygur et al., 2020). In fact, it has been reported that DN targeting MTrPs or the adjacent muscle outside the MTrP area have similar results in post-stroke shoulder pain (Hernandez-Ortiz et al., 2020). Mechanisms of pain reduction after DN may involve both local (peripheral) (Cagnie et al., 2012) and central effects (Schliessbach et al., 2012). The local twitch response and mechanical inactivation of the trigger point may result in muscle soreness after the procedure (Dommerholt & Fernández-de-las-

Peñas, 2013), which is detected on the day following needling. Trigger point dry needling results in local muscle microtrauma and may disrupt dysfunctional endplates (Gerber et al., 2015), causing an involuntary spinal cord reflex contraction of the muscle fibers in a taut band (local twitch response), clearing the excessive buildup of acetylcholine (Cagnie et al., 2013). While the acute effects on DN over the MTrPs can be immediate, the biochemical changes responsible for the specific effects of needling (Shah & Gilliams, 2008) compared to shallow treatment by the sham procedure may take hours to days to build up. Some trials have found that deep dry needling is associated with clinically meaningful results for pain and functionality in the short-term with a single session of active and latent MTrP DN (Calvo-Lobo et al., 2018) and at six months follow-up after up to 4 sessions of DN (Cerezo-Tellez et al., 2016).

Growing evidence suggests that deep muscle DN *per se*, irrespective of its effects in MTrPs, may also decrease pain. Indeed, our results further suggested a different main mechanism driving the analgesic effects of dry needling in pain MPS relief, since the main effects occurred after 2 days of the procedure, which would not be expected it treatment of the trigger point were the sole and main responsible for its analgesic effects. We hypothesized that DN might trigger conditioned pain modulation responses, inducing analgesia via descending inhibition. Alternatively, DN may modulate pain by reducing substance P and CGRP concentrations and increasing the release of endogenous opiates such as beta-endorphin, enkephalin, and dynorphin in nociceptive pathways, causing a decrease in hyperalgesia that would buildup in days (Cagnie et al., 2013). Also, it has also been suggested that acupuncture (and possibly DN) may engage serotoninergic descending pain inhibitory pathways (Schliessbach et al., 2012), with effects of needling in the release of neuropeptides on serotoninergic neurons due to activation of enkephalin-interneurons (Chou et al., 2012) that could not take place immediately after needling.

The dry-needling procedure is very similar to the ancient "ashi" point acupuncture technique, where an acupuncture needle is inserted into the painful area, irrespective of the presence of MPS or trigger points locally. Early Chinese physicians proposed that targeting painful areas leads to a reduction in muscle tenderness. Our QST results further support the idea of the DN effect dissociated from the acute effects on MTrPs. Dry needling did lead to a significant reduction in mechanical hyperalgesia area over the painful area right after needling, which also persisted until the 7th day of follow-up. These suppressive effects in secondary hyperalgesia over referred pain area were expected and were already reported. However, these changes did not correlate with clinical pain relief. This data further suggests that acute DN effects on MTrPs and secondary hyperalgesia were independent of the procedure's long-term clinical analgesic properties. While previous studies have suggested that DN effects in sensory thresholds would correlate with pain relief (Hsieh et al., 2007), these reports were not based on a broader QST assessment. We believe our findings were due to the use of two control areas for QST in the present study: the contralateral mirror area over the contralateral shoulder and an ipsilateral area over the trunk. We undertook the two-control area approach based on the finding that shoulder pain is bilateral in at least 41% of patients (Burner et al., 2014) and this would bias a solely contralateral assessment of QST abnormalities. This methodological choice probably reduced local sensory changes occurring with time and provided a more adapted and specific control area.

Considering the importance of blinding in clinical research, and that dry needling is an interventional treatment, adequate participant blinding has been challenging in interventional trials (Chen et al., 2021). A systematic review evaluated 19 randomized controlled trials of high quality on dry needling in MSK pain in general. Only 10 (52%) included a sham intervention, and only 3 of them actually assessed the quality of blinding (Boyles et al., 2015). Our blinding assessment demonstrated that patients could not accurately tell which treatment

group they were allocated into, indicating an adequate blinding. To the best of our knowledge, this was the first study to standardize, describe in detail, control for pain during the sham and active procedure, and film the needling intervention, which, we believe, was a major positive methodological improvement.

Our study had some limitations that should be considered in interpreting these results. The treatment of chronic MPS usually requires a course of treatment, and not only one single intervention (Dommerholt & Fernández-de-las-Peñas, 2013). Also, since we stopped our assessment on the 7th day after needing, we do not know the analgesic effect's exact time duration. Additionally, dry needling is rarely used as a monotherapy in clinical practice, and its effect in multimodal real-life treatment approaches remains to be determined.

Our results suggest a pragmatic next step in trials on DN for pain. Since the analgesic effects persisted for at least seven days after the procedure, this may impact the dosing of next studies proposing DN as a long-term treatment approach for MPS. One could propose that weekly DN sessions should be used instead of daily session protocols that are costly and decrease treatment compliance.

7 CONCLUSIONS

7. CONCLUSIONS

This randomized controlled trial demonstrated analgesic effects of local dry needling in shoulder pain for patients with chronic shoulder pain due to myofascial pain syndrome. Active trigger points dry needling provided analgesic effects compared with sham and decreased the area of local mechanical hyperalgesia as evaluated through quantitative sensory testing.

The effects persisted for at least seven days after treatment. These findings suggest that dry needling for shoulder pain could have practical clinical implications and may provide mechanistic insights behind MPS.

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9 APPENDICES

APPENDIX A

ESCALA VISUAL ANALÓGICA

Assinale abaixo o valor que corresponde a sensação de dor existente neste momento. O valor mínimo de 0, corresponde a ausência de dor, e o valor máximo de 10, corresponde a uma dor insuportável, para você como nunca antes sentida.

0 1 2 3 4 5 6 7 8 9 10

sem dor dor máxima

APPENDIX B

QUESTIONÁRIO DE AVALIAÇÃO DE DOR NEUROPÁTICA – DN4

Complete este questionário marcando a resposta a cada item das questões abaixo

1 Quais são as características da dor do seu paciente ?

	SIM	NÃO
Queimação		
Frio		
Choques elétricos		

2 No local onde a dor do seu paciente incide, ele sente um ou mais desses sintomas

	SIM	NÃO
Formigamento		
Agulhadas		
Dormência		
Coceira		

3 No local onde a dor do seu paciente incide ao exame físico, você encontrou algumas dessas características ?

	SIM	NÃO
Hipoestesia ao toque		
Hipoestesia ao estímulo com agulha		

4 No local onde a dor do seu paciente incide, a dor pode aumentar com:

	SIM	NÃO
Contato com um pincel ou escova		

RESULTADO: 1 ponto para cada SIM e 0 ponto para cada NÃO. Se o total for igual ou maior que 4, o teste é positivo para dor neuropática (sensibilidade 82,9% e especificidade de 89,9%)

APPENDIX C

GRUPO DE DOR – IOT /HCFMUSP

Data:___/___/_____

HAD

Nome:_____REG:_____
Idade:____ Sexo:____ Nasc:____/___/_____ Est. Civ:_____Profissão:_____
Diagnóstico:_____telefone:_____

Por favor, leia todas as frases. Marque com um "X" a resposta que melhor corresponder a como você tem se sentido na última semana.
Não é preciso ficar pensando muito em cada questão. Vale mais a sua resposta espontânea.

A - **Eu me sinto tenso ou contraído**
3 ( ) A maior parte do tempo
2 ( ) Boa parte do tempo
1 ( ) De vez em quando
0 ( ) Nunca

D – **Eu ainda sinto gosto (satisfação) pelas mesmas coisas de que costumava gostar**
0 ( ) Sim, do mesmo jeito que antes
1 ( ) Não tanto quanto antes
2 ( ) Só um pouco
3 ( ) Já não sinto mais prazer em nada

A – **Eu sinto um espécie de medo, como se alguma coisa ruim fosse acontecer**
3 ( ) Sim, de um jeito muito forte
2 ( ) Sim, mas não tão forte
1 ( ) Um pouco, mas isso não me preocupa
0 ( ) Não sinto nada disso

D – **Dou risada e me divirto quando vejo coisas engraçadas**
0 ( ) Do mesmo jeito que antes
1 ( ) Atualmente um pouco menos
2 ( ) Atualmente bem menos
3 ( ) Não consigo mais

A – **Estou com a cabeça cheia de preocupações**
3 ( ) A maior parte do tempo
2 ( ) Boa parte do tempo
1 ( ) De vez em quando
0 ( ) Raramente

D – **Eu me sinto alegre**
3 ( ) Nunca
2 ( ) Poucas vezes
1 ( ) Muitas vezes
0 ( ) A maior parte do tempo

A – **Consigo ficar sentado á vontade e me sentir relaxado**
0 ( ) Sim, quase sempre
1 ( ) Muitas vezes
2 ( ) Poucas vezes
3 ( ) Nunca

D – **Estou lento (lerdo) para pensar e fazer as coisas**
3 ( ) Quase sempre
2 ( ) Muitas vezes
1 ( ) De vez em quando
0 ( ) Nunca

A – **Tenho uma sensação ruim de medo (como um frio na espinha ou um aperto no estômago)**
0 ( ) Nunca
1 ( ) De vez em quando
2 ( ) Muitas vezes
3 ( ) Quase sempre

D – **Eu perdi o interesse em cuidar da minha aparência**
3 ( ) Completamente
2 ( ) Não estou mais me cuidando como eu deveria
1 ( ) Talvez não tanto quanto antes
0 ( ) Cuido-me do mesmo jeito que antes

A – **Eu me sinto inquieto, como se eu não pudesse ficar parado em nenhum lugar**
3 ( ) Sim, demais
2 ( ) Bastante
1 ( ) Um pouco
0 ( ) Não me sinto assim

D – **Fico esperando animado s coisas boas que estão por vir**
0 ( ) Do mesmo jeito que antes
1 ( ) Um pouco menos que antes
2 ( ) Bem menos do que antes
3 ( ) Quase nunca

A – **De repente, tenho a sensação de entrar em pânico**
3 ( ) A quase todo momento
2 ( ) Várias vezes
1 ( ) De vez em quando
0 ( ) Não sinto isso

D – **Consigo sentir prazer ao assistir a um bom programa de TV, de rádio ou quando leio alguma coisa**
0 ( ) Quase sempre
1 ( ) Várias vezes
2 ( ) Poucas vezes
3 ( ) Quase nunca

Psicólogo:_____

APPENDIX D

Impressão Clínica Global - ICG (versão do paciente)

- Após o tratamento eu estou:

  1) muito melhor;

  2) melhor;

  3) ligeiramente melhor;

  4) sem alterações;

  5) ligeiramente pior;

  6) pior;

  7) muito pior.

- Escala a ser respondida no último dia de cada sessão.

Impressão Clínica Global (versão do avaliador)

- Após o tratamento eu estou:

  1) muito melhor;

  2) melhor;

  3) ligeiramente melhor;

  4) sem alterações;

  5) ligeiramente pior;

  6) pior;

  7) muito pior.

- Escala a ser respondida no último dia de cada sessão.

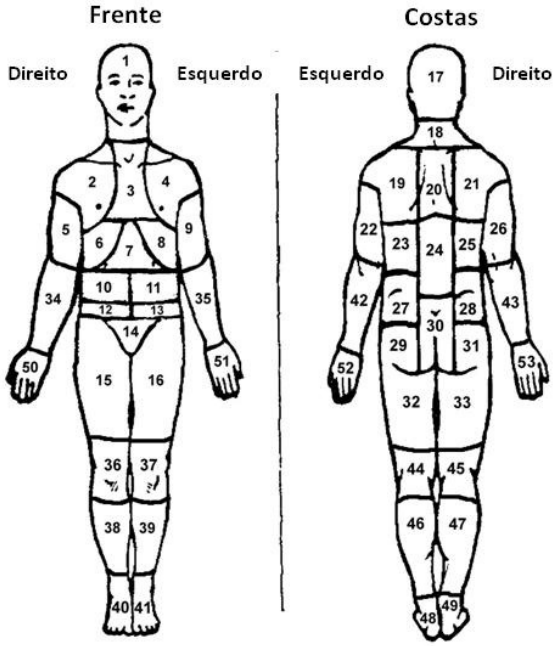
APPENDIX E

INVENTÁRIO BREVE DE DOR

1) Durante a vida, a maioria das pessoas apresenta dor de vez em quando (dor de cabeça, dor de dente, etc.). Você teve hoje, dor diferente dessas?

1.Sim ☐ 2.Não ☐

2) Marque sobre o diagrama, com um X, as áreas onde você sente dor, e onde a dor é mais intensa.



3)Circule o número que melhor descreve a pior dor que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

4) Circule o número que melhor descreve a dor mais fraca que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

5) Circule o número que melhor descreve a média da sua dor.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

6) Circule o número que mostra quanta dor você está sentindo agora (neste momento).

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

7) Quais tratamentos ou medicações você está recebendo para dor?		
Nome	**Dose/ Freqüência**	**Data de Início**

8) Nas últimas 24 horas, qual a intensidade da melhora proporcionada pelos tratamentos ou medicações que você está usando?

Circule o percentual que melhor representa o alívio que você obteve.

Sem alívio | 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% | alívio completo

9) Circule o número que melhor descreve como, nas últimas 24 horas, a dor interferiu na sua:

Atividade geral

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Humor

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Habilidade de caminhar

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Trabalho

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Relacionamento com outras pessoas

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Sono

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Habilidade para apreciar a vida

Não interferiu | O 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

APPENDIX F

Nome:_____ RGHC_____ Data:___/___/___

Questionário de dor McGILL

Algumas palavras que eu vou ler descrevem a sua dor atual. Diga-me quais palavras melhor descrevem a sua dor. Não escolha aquelas que não se aplicam. Escolha somente uma palavra de cada grupo. A mais adequada para a descrição de sua dor.

SENSORIAL

1	2	3	4	5
1 – vibração 2 – tremor 3 – pulsante 4 – latejante 5 – como batida 6 – como pancada	1 – pontada 2 – choque 3 – tiro	1 – agulhada 2 – perfurante 3 – facada 4 – punhalada 5 – em lança	1 – fina 2 – cortante 3 – estraçalha	1 – beliscão 2 – aperto 3 – mordida 4 – cólica 5 – esmagamento

6	7	8	9	10
1 – fisgada 2 – puxão 3 – em torção	1 – calor 2 – queimação 3 – fervente 4 – em brasa	1 – formigamento 2 – coceira 3 – ardor 4 – ferroada	1 – mal localizada 2 – dolorida 3 – machucada 4 – doída 5 – pesada	1 – sensível 2 – esticada 3 – esfolante 4 – rachando

AFETIVO

11	12	13	14	15
1 – cansativa 2 – exaustiva	1 – enjoada 2 – sufocante	1 – castigante 2 – atormenta 3 – cruel	1 – amedrontadora 2 – apavorante 3 – aterrorizante 4 – maldita 5 – mortal	1 – miserável 2 – enlouquecedora

AVALIATIVO

16
1 – chata 2 – que incomoda 3 – desgastante 4 – forte 5 – insuportável

MISCELÂNEA

17	18	19	20
1 – espalha 2 – irradia 3 – penetra 4 – atravessa	1 – aperta 2 – adormece 3 – repuxa 4 – espreme 5 – rasga	1 – fria 2 – gelada 3 – congelante	1 – aborrecida 2 – dá náusea 3 – agonizante 4 – pavorosa 5 – torturante

Número de descritores	**Índice de dor**
Sensorial:	Sensorial:
Afetivo:	Afetivo:
Avaliativo:	Avaliativo:
Miscelânea:	Miscelânea:
TOTAL:	TOTAL:

APPENDIX G

Ficha 1: TRIAGEM

1. Paciente **Sem** fibromialgia?

2. Maior que 18 anos de idade?

3. Dor no ombro e/ou no braço de origem miofascial de duração superior a três meses?

Se sim em todos os itens, anotar o nome do paciente e 3 telefones para contato

	Nome	3 telefones para contato
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		

APPENDIX H

Ficha 2: Inclusão (Dra Helena) [D -7]

Nome: _____

Idade: ____ Peso: ____Kg Altura: _____m Data: _____ /_____ /_____

EVA ombro Direito:	EVA ombro Esquerdo:

Assimetria da dor? Sim ☐ Não ☐

DN4 < 4? Sim ☐ Não ☐

Dor superior a 3 meses com VAS ≥ 4? Sim ☐ Não ☐

Ponto gatilho mais sintomático: _____

Tratamento medicamentoso estável (por mais de 15 dias)? Sim ☐ Não ☐

Se sim, quais?

Medicamento para dor	Dose diária

Depressão (DSN4) ? Sim ☐ Não ☐

Dor intermitente? Sim ☐ Não ☐

Paciente tem disponibilidade de vir nas visitas? Sim ☐ Não ☐

RANDOMIZAÇÃO: GRUPO (ativo/Sham)_____

Entregar para o paciente o formulário para preenchimento do EVA diário e orientá-lo como preenchê-lo a a trazê-lo na semana seguinte.

APPENDIX J

Ficha 3: Avaliação Sensitiva

Nome: _____

Data: _____ /_____ /_____

D 0 pré ☐ D 0 pós ☐ D + 7 ☐

	Trapézio E	Trapézio D	Área controle[1]
Lado da dor			
Limiar detecção tátil (número)			
Limiar de dor mecânica (número)			
Estimulação supra laminar (limiar de dor mecânica + 4 (EVA em mm)			
Estimulação supra laminar (limiar de dor mecânica + 6 (EVA em mm)			
Presença de alodínea mecânica dinâmica? Se sim, anotar VAS			
Hiperalgesia no local da dor? (VAS com 19)			
Área de hiperalgesia (medir no lado da dor somente)			
Estimulação dolorosa térmica (VAS) Temperatura frio: 9-11º			
Estimulação dolorosa térmica (VAS) Temperatura quente:			

1: area controle: dez centímetros abaixo do trapézio, perto do ângulo da escápula

Hiperalgesia: VAS > 20%

APPENDIX K

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .:..... .....

DOCUMENTO DE IDENTIDADE Nº : ..... SEXO : .M ☐ F ☐
DATA NASCIMENTO: ...../...../.....
ENDEREÇO ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE .....
CEP:..... TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL .....
NATUREZA (grau de parentesco, tutor, curador etc.) .....

DOCUMENTO DE IDENTIDADE :.....SEXO: M ☐ F ☐
DATA NASCIMENTO.: ...../...../.....
ENDEREÇO: ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE: .....
CEP: ..... TELEFONE: DDD (.....).....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA

Avaliação da eficácia do agulhamento seco no tratamento da Síndrome Dolorosa Miofascial e seus efeitos sobre a sensibilidade local.....

PESQUISADOR RESPONSÁVEL: Prof. Dr. Manoel Jacobsen Teixeira INSCRIÇÃO CONSELHO REGIONAL Nº 17968

CARGO/FUNÇÃO: Professor Titular de Neurocirurgia, Departamento de Neurologia.

PESQUISADOR EXECUTANTE: Dr. Daniel Ciampi de Andrade INSCRIÇÃO CONSELHO REGIONAL Nº 108232
CARGO/FUNÇÃO: Médico assistente

UNIDADE DO HC-FMUSP: Divisão de Neurologia, Instituto Central.

3. AVALIAÇÃO DO RISCO DA PESQUISA:

RISCO MÍNIMO X RISCO MÉDIO ☐

RISCO BAIXO ☐ RISCO MAIOR ☐

4.DURAÇÃO DA PESQUISA : 24 meses

1 – Desenho do estudo e objetivo(s)

Um dos principais tratamentos da Síndrome Dolorosa Miofascial consiste na infiltração à seco dos pontos gatilho. Estamos solicitando a sua participação voluntária neste estudo que tem por objetivo avaliar tanto o alivio analgésico proporcionado pela infiltração do músculo trapézio quanto a sensibilidade do local infiltrado.

2 – Descrição dos procedimentos que serão realizados, com seus propósitos e identificação dos que forem experimentais e não rotineiros;

O Sr(a). está sendo convidado a participar de um estudo para verificar se essa infiltração do ponto gatilho vai ajudar a diminuir a sua dor que tem mais de 3 meses, de intensidade moderada a forte, localizada em apenas um lado do ombro, presente diariamente ao mínimo de 4 dias por semana. Utilizaremos questionários que caracterizem de forma mais detalhada a sua dor, o impacto dela na sua vida com duração de uns 30 minutos. Vale lembrar que todos os procedimentos são os de rotina na clínica de dor do hospital, conhecidos e testados anteriormente.

3 – Relação dos procedimentos rotineiros e como são realizados –

O seu médico irá orientá-lo para comparecer ao hospital 3 vezes. Na primeira visita, o Sr(a). será avaliado e será orientado a preencher um diário da dor nos próximos 7 dias. Na segunda consulta, o Sr(a). responderá uns questionários e receberá a infiltração à seco dos pontos gatilho, além de testes quantitativos da sensibilidade antes e depois da infiltração. Depois de 7 dias preenchendo o diário de dor após a infiltração, o Sr(a) retornará para uma última aplicação dos questionários e testes da sensibilidade, compondo portanto, um total de 14 dias sob avaliação da dor pelo nosso estudo. É muito importante que o Sr(a). mantenha inalterado o tratamento prévio durante as duas semanas do nosso estudo.

4 – Descrição dos desconfortos e riscos esperados nos procedimentos dos itens 2 e 3;

O Sr(a). poderá sentir algum incomodo no momento da infiltração da agulha e seria muito útil para nosso estudo, se o sr(a) pudesse nos quantificar esse desconforto também. Todos os cuidados serão tomados para evitar qualquer complicação e o seu médico estará ao seu lado durante toda a sessão que poderá ser interrompida por qualquer motivo, a qualquer momento.

5 – Benefícios para o participante

O Sr(a). pode beneficiar-se com a melhora da dor, do sono e do estado de ânimo. O Sr(a). continuará recebendo o tratamento habitual mas ao mesmo tempo estará colaborando para possíveis avanços no tratamento de pessoas que também tenham dores como a sua e contribuirá para o melhor entendimento médico da Síndrome Dolorosa Miofascial.

6 –O Sr(a). pode optar a qualquer momento a interromper o estudo. Estaremos também sempre disponíveis para esclarecimentos de dúvidas e questões que surjam antes, durante, ou depois da pesquisa.

7 – Em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é Dr. Daniel Ciampi de Andrade, que pode ser encontrado no Serviço de Neurologia do HC FMUSP (quinto andar do Instituto Central Av Dr Enéas de Aguiar 255 Pinheiros SP . Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5º andar – tel: 3069-6442 ramais 16, 17, 18 ou 20, FAX: 3069-6442 ramal 26 – E-mail: cappesq@hcnet.usp.br

8 – É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição;

09 – Direito de confidencialidade –
As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgado a identificação de nenhum paciente;

10 – Direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

11 – Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação. Se existir qualquer despesa adicional, ela será absorvida pelo orçamento da pesquisa.

12 – Em caso de dano pessoal, diretamente causado pelos procedimentos ou tratamentos propostos neste estudo (nexo causal comprovado), o participante tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas.

13 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo.

Eu discuti com o Dr _____ sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

_____

Assinatura do paciente/representante legal Data ___/___/___

_____

Assinatura da testemunha Data ___/___/___

(para casos de pacientes menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual.)

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

_____

Assinatura do responsável pelo estudo Data ___/___/___

APPENDIX L

HC

APROVAÇÃO

A Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq da Direforia Clínica do Hospital das Clínicas e da Faculdade de Medicina da Universidade de São Paulo, em sessão de 08/09/2010, **APROVOU** o Protocolo de Pesquisa nº **0447/10**, intitulado: "**AVALIAÇÃO DA EFICÁCIA DO AGULHAMENTO SECO NO TRATAMENTO DA SÍNDROME DOLOROSA MIOFASCIAL E SEUS EFEITOS SOBRE A SENSIBILIDADE LOCAL**" apresentado pelo Departamento de **NEUROLOGIA**, inclusive o Termo de Consentimento Livre e Esclarecido.

Cabe ao pesquisador elaborar e apresentar à CAPPesq, os relatórios parciais e final sobre a pesquisa (Resolução do Conselho Nacional de Saúde nº 196, de 10/10/1996, inciso IX.2, letra "c").

Pesquisador (a) Responsável: **Prof. Dr. Manoel Jacobsen Teixeira**

Pesquisador (a) Executante: **Dr. Daniel Ciampi de Andrade**

CAPPesq, 09 de Setembro de 2010

Prof. Dr. Eduardo Massad
Presidente da Comissão de Ética para Análise de Projetos de Pesquisa

Comissão de Ética para Análise de Projetos de Pesquisa do HCFMUSP e da FMUSP Diretoria Clínica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo Rua Ovídio Pires de Campos, 225, 5º andar - CEP 05403 010 - São Paulo – SP Fone: 011 3069 6442 Fax: 011 3069 6492 e-mail: cappesq@hcnet.usp.br / secretariacappesq2@hcnet.usp.br

10 PUBLICATIONS ARISING FROM THIS THESIS

Milan2012
14TH WORLD CONGRESS ON PAIN®

CERTIFICATE OF PRESENTATION

The following poster was submitted and presented at the 14th World Congress on Pain, held at the Milano Convention Center in Milan, Italy, August 27-31, 2012.

PF 406

EVALUATION OF THE EFFICACY AND TEMPORAL PATTERN OF DRY NEEDLING IN THE TREATMENT OF MYOFASCIAL PAIN SYNDROME

Marcus Y. B. Pai, Juliana T. Toma, Irina Raicher, Helena H. S. Kaziyama, Ricardo Galhardoni, Manoel J. Teixeira, Daniel C. A. Andrade,

The 14th World Congress on Pain is organized by the International Association for the Study of Pain.

Presented: 8/31/2012

Irene Tracey,
Chair, Scientific Program Committee

General Section
Research Paper

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PAIN REPORTS®

Dry needling has lasting analgesic effect in shoulder pain: a double-blind, sham-controlled trial

Marcus Yu Bin Pai[a,b], Juliana Takiguti Toma[a], Helena Hideko Seguchi Kaziyama[a,b], Clarice Listik[a], Ricardo Galhardoni[a], Lin Tchia Yeng[a,b,c], Manoel Jacobsen Teixeira[a,c], Daniel Ciampi de Andrade[a,c,*]

Abstract

Introduction: Myofascial pain syndrome (MPS) affects most patients with chronic shoulder pain. Dry needling (DN) is a common treatment for MPS, but its temporal pattern and sensory effects remain unknown. We evaluated in a randomized, sham-controlled study the pattern of analgesic efficacy and local sensory changes of a single session of DN for MPS in patients with chronic shoulder pain.

Methods: Patients with chronic shoulder pain were randomized into active (n = 20) or sham (n = 21) groups. A single DN was performed by a researcher blinded to group assignment and pain outcomes. Pain intensity was assessed by the numeric rating score, and sensory thresholds were evaluated with a quantitative sensory testing protocol, including the area of tactile sensory abnormalities 7 days before needling, right before, and 7 days after the intervention.

Results: Dry needling led to significant larger pain intensity reduction (from 6.30 ± 2.05 to 2.40 ± 2.45 in the active group; $P = 0.02$, effect size = −1.3 (95% CI [−2.0 to −0.68]); (number necessary to treat = 2.1). Pain reduction scores were significantly different on the second day after needling and persisted so until the seventh day and were accompanied by improvement in other dimensions of pain and a decrease in the area of mechanical hyperalgesia in the active DN group alone ($P < 0.05$).

Conclusion: Active trigger points DN provided analgesic effects compared with sham and decreased the area of local mechanical hyperalgesia. These findings have practical clinical implications and may provide mechanistic insights behind MPS.

Keywords: Myofascial pain, Chronic pain, Dry needling, Trigger points, Shoulder pain, Quantitative sensory testing

1. Introduction

Musculoskeletal pain disorders rank as the 10th leading cause of years lived with disability worldwide.[27] Shoulder pain is responsible for up to 20% of musculoskeletal complaints,[39,52] leading to inability to work, loss of productivity, and a considerable burden for the patient and society.[43] Shoulder pain is a common complaint in all ages, and it is one of the major reasons why patients consult with primary health care providers.[23,43] The lifetime prevalence of shoulder disorders may affect up to 70% of the population.[8]

Myofascial pain syndrome (MPS) is characterized by local and referred pain because of the occurrence of tenderness in a taut, palpable band of muscle fibers, where painful hyperalgesic myofascial trigger points (MTrP) are identified by manual palpation.[32] Myofascial trigger points occur due to dysfunctional endplate potential and excessive acetylcholine release in the neuromuscular junction that prevents muscle fibers from fully relaxing. It usually arises from muscle overload secondary to inadequate postures or overuse from repetitive activities or as part of referred pain from deeper injured structures, resulting in increased local tenderness and pain.[9,21,30]

Myofascial pain syndrome is highly prevalent and is considered one of the most common mechanisms behind shoulder disorders, affecting up to 95% of patients.[50] Myofascial pain syndrome is frequently found in nociceptive shoulder pain and is believed to be the main cause of pain or coexist and contribute to shoulder pain occurring due to other etiologies, such as subacromial impingement syndrome bursitis, and rotator cuff syndrome.[6] Myofascial pain syndrome is associated with disability and dysfunction because of decreased range of motion of the girdle joints.[6]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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A variety of therapeutic techniques have been proposed to treat trigger points and MPS.[37] Nonpharmacological approaches are widely used[50] and generally preferred over pharmacological ones because of better tolerance and safer adverse event profiles.[18] Dry needling (DN) is a minimally invasive procedure, consisting of the use of a fine, solid filiform needle repetitively inserted into the fascia and muscle in a fan-like technique (Video S1, available at http://links.lww.com/PR9/A112; Supplemental Digital Content 1, available at http://links.lww.com/PR9/A111). Techniques analogous to DN have been used for over a century in Western Medicine (see description from Sir William Osler in *Principles and Practice of Medicine* in 1912).[30] Dry needling is believed to cause musculoskeletal pain relief[32] and improvement in range of motion by triggering a local twitch response,[1] subsequently leading to a temporary attenuation or disappearance of MTrPs. The dry needling of MTrPs can result in a mechanical reduction of peripheral nociceptive inputs from the muscles,[9] contributing to peripheral, spinal, and supraspinal desensitization, along with activation of multiple central pain regulatory pathways,[21] and functional restoration of neuromyofascial tissues.[9] Dry needling reduces the irritability of neuromuscular junctions (motor endplate noise)[2] and sympathetic overactivity in the affected regions, effectively reducing the overlap of the contractile proteins and relaxing the sarcomeres.[49] Dry needling is usually performed at active MTrPs.[21,37] It is believed that treatment of the trigger point, and thus removal of the peripheral source of nociceptive stimulus can reduce mechanical hyperalgesia and allodynia, as observed in migraine[31] and whiplash.[25] Although needling of MTrPs is part of the daily practice of physicians dedicated to the treatment of musculoskeletal pain, there is still limited clinical evidence for its actual efficacy, as few clinical trials have evaluated its effects in chronic shoulder pain[18,28] against a proper sham needling[17,38] and for a sufficient length of time.

The purpose of this study was to evaluate the actual analgesic effects of a DN session on shoulder pain associated with MPS in a double-blind controlled study. We have also explored the concomitant changes in cutaneous sensory thresholds with a battery of quantitative sensory testing (QST) in the area of referred pain triggered caused by DN (eg, secondary hyperalgesia reduction) and its potential role in predicting the temporal persistence of the analgesic effects caused by the needling procedure.

2. Methods

2.1. Study design

This study was designed as a 2-parallel arm, randomized, and sham-controlled trial, with an allocation ratio of 1:1. The study was approved by our institution's ethics review board (# 0447/10), and all patients provided written informed consent before inclusion in the study. The trial was registered at Clinical Trials (#NCT02179320). Participant enrollment is presented in [F1] **Figure 1**. A total of 74 patients were screened for participation, 43 patients were randomized, 21 for the active and 22 for the sham group.

2.2. Patients

Consecutive patients were recruited in several pain clinics in the area of São Paulo, Brazil, and assessed at the Pain Center of the Hospital das Clinicas of the University of Sao Paulo, Brazil. All patients had chronic nociceptive shoulder pain where MPS[50] was considered to be present and constituted a major cause of pain according to the assessment of 2 independent physiatrists (M.B.P. and J.T.T.). Inclusion criteria included individuals aged 18 to 70 years, presence of chronic unilateral shoulder pain or asymmetrical bilateral shoulder pain, with the most painful side presenting a score of at least 40/100 mm higher in the visual analogue scale (VAS, ranging from 0: no pain to 100: maximal pain imaginable) compared with the less painful shoulder. Other inclusion criteria included the presence of nontraumatic chronic shoulder pain because of at least one of the trapezius muscle trigger points[9] and pain duration longer than 3 months (>15 days per month with pain). Concomitant medication for pain and sleep disorders was allowed, provided that their doses were stable for at least 30 days before enrollment and remained unchanged during the study. Patients were not included if evidence of neuropathic pain was present (ie, a positive *Douleur Neuropatique*-4), if they had intermittent pain patterns (<15 days per month), if they refused to provide consent for participation, or if they had evidence of another painful shoulder disorder such as subacromial impingement syndrome, adhesive capsulitis, calcific tendonitis of the rotator cuff, and severe rotator cuff tendon alterations. All patients underwent shoulder radiography and, in some instances, ultrasound examinations to exclude major structural disorders. Patients with known fibromyalgia or rheumatic diseases were excluded.[3,54] Patients with a current primary psychiatric condition, including major depression or major personality disorders according to *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria and a history of drug or alcohol abuse based on the CAGE[40] questionnaire, were excluded. Patients were also excluded if they were to be enrolled in another clinical trial during the study or if they had participated in a clinical trial within the previous 6 months before enrollment. AQ:3

2.3. Experimental design

Randomization was performed through the website www.randomizer.org. Patients were matched according to age and sex in blocks of 6. The active needling group (A) was composed of participants who underwent one session of standardized trigger point dry needling and by the sham group (S) receiving a standardized sham session of dry needling,[48] see supplementary video (Video S1, available at http://links.lww.com/PR9/A112; Supplemental Digital Content 1, which demonstrates standardized treatment procedures, available at http://links.lww.com/PR9/A111).

Patients were assessed in 3 face-to-face visits—D0: 1 week AQ:4 before needling, D7: day of needling, and D14: 1-week postneedling follow-up.

D0—at enrollment, patients were assessed for eligibility. If enrolled, they were instructed to fill in a 14-day pain diary in which the worst, average, and lowest daily pain intensities were recorded, using the self-rating eleven-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst pain) from the AQ:5 Brief Pain Inventory (BPI),[15,24] to establish a baseline pain level before needling. Patients were also instructed to record any adverse events of the therapy during the study period.

D7—patients were randomly assigned into 2 treatment arms (active or sham treatment). They filled in a preprocedure pain and mood assessment battery. Quantitative sensory testing was performed at 3 sites before and right after the needling procedure at the (1) skin area over the painful trapezium, (2) the contralateral mirror area, and (3) a control area on the trunk (dermatomes T6-8 over of the rib cage, at a site with no local or referred pain) (Table S1, Supplemental Digital Content 2, which demonstrates

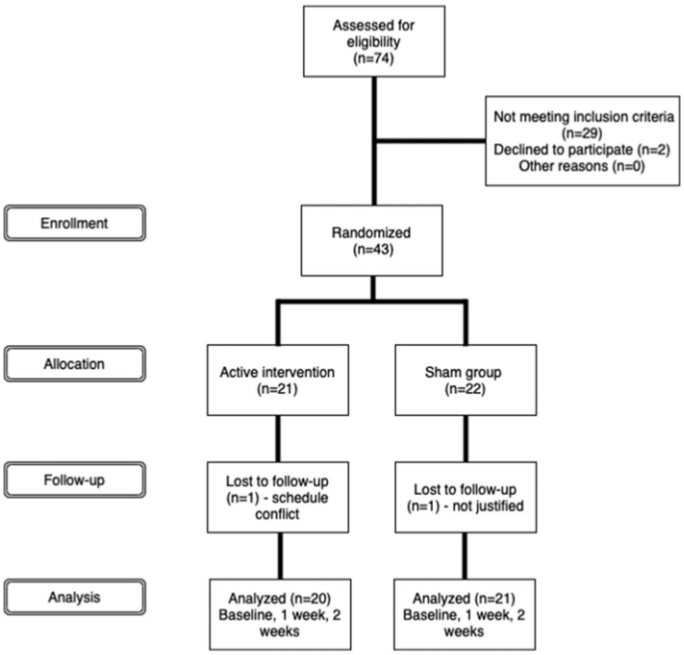

Figure 1. Participant enrollment.

experimental study outline design, available at http://links.lww.com/PR9/A111).

D14—a third QST battery was performed, and the same pain and mood assessment from baseline were filled in.

2.4. Description of the needling procedure

Patients were blinded to which treatment they received. Patients underwent either an active or sham trigger point dry needling to the most painful trapezius muscle. The trigger point was previously localized by firm digital pressure through palpation of the trapezius muscle and pressure algometers with a 3 cm^2 hard foam tip to provide blunt-ended pressure of at least 2 kg/cm^2 (Wagner Instruments). The identification was based on the operational definition of MTrPs by locating the presence of a palpable taut band and its hypersensitive area and a local pain response because of the palpation of the taut band or reproduction of referred pain (defined as 80% resemblance) in response to local digital compression.[42] Patients were seated facing a research assistant, with minimal interpersonal interaction, and needling was performed by a specialist facing the patients' back. The researcher performing the needling procedure had no other role in the study or contact with patients except for the few seconds of the needling procedure duration. Each patient was treated only once. The pain specialist who performed the procedures had to certify that both treatments had the same 20-second duration and were similar in the intensity of transprocedural pain elicited, which was controlled by the measurement of pain intensity on a VAS (0-no pain and 100 mm-maximum pain imaginable) every 5 seconds during needling using a chronometer. The patients were asked to use the hand contralateral to the painful trapezius under treatment to score the VAS. The trigger point inactivation on the active group was performed according to the technique standardized by Simons et al., with 0.25 × 40 mm Huanqiu acupuncture needles. Patients who underwent sham treatment had the needle inserted intradermally, superficially, parallel to the skin, without reaching the muscle and its trigger point. The sham needling technique included twisting the needle in a plane parallel to the fascia so that some pain could be elicited from the procedure but without having the needle inserted into the muscle's trigger point (ie, the putative mechanism of action of active needling) (Video S1, available at http://links.lww.com/PR9/A112; Supplemental Digital Content 1, available at http://links.lww.com/PR9/A111).

2.5. Main clinical endpoints

The primary outcome was pain intensity: average pain intensity over the last 24 hours, measured with an eleven-point numerical rating scale—NRS (0 = no pain and 10 = maximum pain imaginable)—7 days after the procedure (D14). Baseline average pain intensity was assessed with the average pain of the 7 days before needling (from day 1 until 7 = baseline), on the day of the procedure (D7, before dry needling), and daily on the remaining 7 days (until day 14). The secondary aim was to assess whether the analgesia because of dry needling correlated with acute DN-related alterations in mechanical hyperalgesia area and other sensory variables, such as cold-induced pain, mechanical hyperalgesia, or mechanical hyperesthesia.

2.6. Outcome measurements

(1) The VAS is a self-report pain scale, consisting of a horizontal line of 100 mm in length, that is anchored by the ratings "no pain" at the left side (score 0) and "worst pain imaginable" at the right side (score 100).[16]
(2) The numerical rating scale is a self-rating subjective pain measuring scale that measures pain from 0 (no pain) to 10 (worst pain).[22]
(3) The *Douleur Neuropatique*-4 (DN4) questionnaire used for the screening of neuropathic pain.[4,46]
(4) The BPI allows patients to rate the intensity of their pain and pain interference with daily activities.[15,24]
(5) The short-form McGill Pain Questionnaire consists of 15 descriptors, which evaluate sensory, affective, and cognitive aspects of pain.[41]
(6) The Hospital Anxiety and Depression Scale, a self-assessment scale, was used to evaluate the treatment effects on mood and anxiety.[55]

The global impressions of change consist of a Likert scale with 7 points ranging from "very much improved" to "very much worse" based on the degree perception of change after treatment experienced by the patient and the rater (clinician).[22] Patients were classified as "improved" or "not improved" with improvement being a significant or moderate improvement and "not improved" being any other score.

2.7. Quantitative sensory testing

All participants underwent a QST battery over the painful referred pain on the shoulder, a contralateral mirror area, and an area located ipsilateral to the pain side, over the T6-7 dermatomes over the flank. Quantitative sensory testing changes were compared between sessions at the painful side. The QST battery assessed large fiber (Aβ) and small (Aδ and C) mediated somatic sensory inputs, assessed at 3 time points: before DN, immediately after DN, and on D14 (7 days after the procedure). Evaluation of mechanical static tactile sensitivity was performed with calibrated von Frey monofilaments ranging from 0.008 to 300 g (Senselab Aesthesiometer; Somedic, Sweden), of increasing thicknesses, for determining the threshold of tactile and pain detection, exerting greater pressure on the skin as the monofilament caliber increased. The detection of pain thresholds, supraliminal stimulations with strands 2 and 3 times thicker than the ones used for determining pain threshold was made so that mechanical hyperalgesia was evaluated through the VAS after each stimulus. Finally, the mechanical hyperalgesia area (cm^2) boundaries were determined with suitable von Frey filaments[44] and marked using a proper nontoxic pen. This area was then copied through transparent paper, scanned, and digitally quantified in the computer with Adobe Photoshop CS4 11.0. For thermal nonpainful perception and cold hyperalgesia, a custom-made contact thermode (USP, 2016) was applied over the painful trapezius muscle at 2 constant fixed temperatures of 15 and 5°C for 5 seconds.

2.8. Safety

The safety of dry needling was assessed by monitoring the occurrence of adverse effects during treatment by a dedicated recording file.

2.9. Blinding assessment

The blinding assessment was evaluated with a 4-question form, which asked patients whether they knew which group they were, which intervention they received, their pain intensity during needling, and if they would accept receiving the same treatment again if proposed and their justification.[45]

2.10. Statistical analyses

Statistical analyses were conducted with SPSS version 22 (SPSS Inc, Chicago, IL). The categorical data were expressed in proportions, and continuous variables were expressed in mean and standard deviation. The exploratory analysis initially evaluated distributions, frequencies, and percentages for each of the numeric and categorical variables. We assessed randomization effectiveness by evaluating balance regarding baseline variables, comparing the interventional and the control arms. Normality of the data was accessed by the Kolmogorov–Smirnoff test. In all cases, P values <0.05 were considered significant. The repeated-measures analysis of variance test was used for the comparison of the outcomes between the groups along the trial, including an interaction term between group and time and post hoc analyses when indicated. Correlation analyses between the main outcome results were performed to verify the association between pain improvement and QST parameters. Only correlations with coefficients above 0.4 were reported. Because the Kolmogorov–Smirnov test revealed that secondary outcomes such as quality of life and QST values did not have a normal distribution, the differences between groups were compared using nonparametric test (Kruskal–Wallis test), followed by pairwise comparisons of change between groups (Wilcoxon/s/Mann–Whitney U-test). Bonferroni correction for multiple comparisons was used in these settings. The sample size was calculated based on the effect size achieved by a previous trial,[51] considering a repeated-measures analysis of variance approach and using the software G*Power 3.1.9.2 for Windows (California). Bearing in mind the assumptions of an effect size of 0.4 (equivalent to an eta squared effect size of 0.140), 2-tailed α error level probability of 0.05, and a minimum power of 0.80, the estimated sample size needed would be 20 subjects per arm. We included 3 extra participants to account for loss of follow-up. Cohen's d, defined as the difference between the means of the 2 groups divided by the pool standard error, was used for the calculation of effect sizes.

3. Results

3.1. Patients

Data collection took place between February 2015 and January 2016. Two patients were lost during follow-up, one from each group. The reasons for dropping out were specified in **Figure 1**. Table S2 (Supplemental Digital Content 3, available at http://links.lww.com/PR9/A111) shows the baseline characteristics of the trial participants. There were no significant differences between treatment groups regarding demographic and pain characteristics at baseline (all P values >0.2). Patients included in this study had an average age of 58, and most were women (82%). All patients were trigger point dry needling naïve.

3.2. Efficacy of dry needling on main outcomes

Dry needling had a significant effect on average pain intensity throughout the treatment, as shown by comparison with the sham group (Table S3, Supplemental Digital Content 4; Figure S1, Supplemental Digital Content 6, available at http://links.lww.com/PR9/A111). The group treated with active needling had

significantly lower pain scores than the sham group at follow-up with an average pain intensity change from 6.30 ± 2.05 before the therapy to 2.40 ± 2.46 at the end of treatment (D14) in the active group and 6.04 ± 1.32 before the treatment to 5.14 ± 1.49 at the end of therapy (D14) in the sham group ($F(1,39) = 5.908$; $P = 0.02$; 95% CI, 1.25 to 3.55, Cohen's d effect size = 1.34 (Cohen, 1988)).

Post hoc analysis with adjustment for multiple testing revealed that the NRS pain score was statistically significantly decreased from baseline to D14 (2.350 [95% CI, 1.781–2.919], $P < 0.001$). There was also a statistically significant difference in NRS at D14 between groups, $F(1, 39) = 74.41$, $P < 0.01$, partial $\eta 2 = 0.317$. There was a statistically significant effect of time on NRS pain for the sham group, $F(1, 20) = 7.211$, $P < 0.014$, partial $\eta 2 = 0.265$, and for the active DN group, $F(1,19) = 55.682$, $P < 0.001$, partial $\eta 2 = 0.746$ (Table S4, Supplemental Digital Content 5, available at http://links.lww.com/PR9/A111).

3.3. Efficacy of dry needling and its immediate effects on pain

One single session of dry needling resulted in significant pain reduction in the BPI-worst and BPI-average pain (Figure S2, Supplemental Digital Content 7, available at http://links.lww.com/PR9/A111) score starting from D9 (2 days after needling) until D14 [T1] (**Table 1**), suggesting a sustained persistent analgesic effect in the active group only during this period. There was a statistically significant interaction between the intervention and time on BPI-average pain reduction from D9 to D14, F (7273) = 3.047, $P = 0.004$, 95% CI, 0.565 to 3.174, and BPI-worst pain reduction from D9 to D14, F (7273) = 2.959, $P = 0.005$, 95% CI 0.591 to 3.223. We found no significant pain reduction for the weakest pain in any of the evaluated days.

3.4. Effects of dry needling on pain secondary outcomes

Active dry needling significantly improved the BPI-pain interference score, with patients reporting a marked decrease in the interference of pain with "general activities," "mood," and "sleep," compared with the sham procedure. Dry needling had a significant effect on MPQ evaluative dimension of pain, but not on affective or sensory ones. Mean anxiety and depression scores measured on the HAD scale were not significantly [T2] affected by DN (**Table 2**). Patients in the active group reported 80.0% and 75.0% of "much improvement" in global impression of change—patient and clinician versions, respectively—compared with 33.3% and 42.9% for the sham group ($P = 0.030$ and $P = 0.037$; respectively), the number necessary to treat = 2.1.

3.5. Effects of dry needling on quantitative sensory testing

Dry needling produced a significant reduction in mechanical hyperalgesia on the skin over the painful area after needling (49.2 ± 37.4 cm^2 at baseline [D7], 39.2 ± 42.7 immediately after needling on D7, and 30.3 ± 28.5 cm^2 on D14, $P = 0.001$), for the active group when compared with sham stimulation. Other QST variables were not affected by treatment (Table S5, Supplemental Digital Content 5, available at http://links.lww.com/PR9/A111).

3.6. Medication use

Patients had an average MQS of 7.50 ± 3.18 in active and 7.14 ± 3.19 in sham groups at baseline ($P = 0.67$). At D14, MQS for the sham group was 6.85 ± 3.08 ($P = 0.55$) and 7.10 ± 3.07 ($P = 0.57$) in the active groups.

3.7. Correlation analyses

As expected, improvement of pain intensity was significantly correlated with an improvement on global impression of change both for patients and clinicians (rho = −0.630, $P = 0.003$, and rho = −0.630, $P = 0.003$, respectively). There was no correlation between BPI-average pain intensity improvement and changes on the area of mechanical hyperalgesia. Interestingly, we found a correlation between daily pain improvement starting 2 days (Figure S3, Supplemental Digital Content 8, available at http://links.lww.com/PR9/A111) after active dry needling and a higher pain reduction during the following days until the last assessment (D10: rho = 0.590, $P = 0.013$; D11: rho = 0.512, $P = 0.21$; D12: rho = 0.772, $P = 0.0001$; D13: rho = 0.752, $P = 0.0001$; and D14: rho = 0.670, $P = 0.001$).

Also, patients who presented an immediate mechanical hyperalgesia area reduction after needling had a positive correlation with maintaining this positive area reduction response after 7 days on D14 (rho = 0.436, $P = 0.004$) (Figure S4, Supplemental Digital Content 9, available at http://links.lww.com/PR9/A111). In addition, patients who had a reduction of the area of mechanical hyperalgesia area had a positive correlation with decreasing mechanical pain threshold at D14 (rho = 0.413, $P = 0.007$) (Figure S5, Supplemental Digital Content 10, available at http://links.lww.com/PR9/A111).

3.8. Adverse events

The dry needling treatment was well tolerated by patients. No major adverse events were reported from any patient included in this trial. Minor side effects such as minor local pain after dry

Table 1

Results of the effects of dry needling on pain.

	Baseline	D8	D9	D10	D11	D12	D13	D14
BPI-worst pain active	6.84 ± 1.58	5.50 ± 3.03	4.65 ± 2.71*	4.50 ± 2.46*	4.65 ± 2.73*	4.25 ± 2.76*	4.05 ± 2.41*	3.95 ± 2.25*
BPI-worst pain sham	7.50 ± 1.33	6.80 ± 2.29	6.66 ± 2.61	6.57 ± 2.18	6.57 ± 2.29	6.23 ± 2.23	6.42 ± 2.71	6.85 ± 2.03
BPI-average pain active	5.11 ± 1.81	4.20 ± 2.82	3.40 ± 2.43*	3.10 ± 1.99*	3.55 ± 2.52*	3.15 ± 2.43*	2.90 ± 1.97*	2.70 ± 1.89*
BPI-average pain sham	5.84 ± 1.76	5.04 ± 2.41	5.23 ± 2.50	5.28 ± 2.72	5.23 ± 2.91	4.90 ± 2.46	5.04 ± 3.02	5.42 ± 2.22
BPI-lowest pain active	3.75 ± 1.68	3.20 ± 2.70	2.60 ± 2.08	2.70 ± 1.89	2.65 ± 2.05	2.45 ± 2.18	2.30 ± 19.2	1.90 ± 1.74
BPI-lowest pain sham	4.35 ± 2.11	4.09 ± 2.32	4.14 ± 2.43	4.00 ± 2.68	4.28 ± 2.41	4.04 ± 2.39	4.14 ± 2.63	5.42 ± 2.22

Values are presented as mean ± standard deviation.

* $P < 0.05$.

BPI, Brief Pain Inventory.

Table 2

AQ:11 AQ:12 **Results of secondary assessments.**

	Baseline (D0)		Effect 1 wk after needling (D14)		*P*	Effect size
	Active	Sham	Active	Sham		
HAD depression	6.55 ± 4.65	7.71 ± 3.67	6.80 ± 3.92	7.66 ± 3.38	0.659	0.005
HAD anxiety	8.25 ± 3.76	10.1 ± 2.71	7.75 ± 3.02	9.61 ± 2.81	0.869	0.001
McGill VAS	6.30 ± 2.05*	6.57 ± 1.74	2.40 ± 2.45*	5.42 ± 1.71	**<0.001**	0.363
McGill sensory	4.40 ± 1.63	4.66 ± 1.52	3.90 ± 2.24	5.00 ± 2.28	0.226	0.037
McGill affective	3.25 ± 1.55	3.57 ± 1.24	2.55 ± 1.76	2.85 ± 1.52	0.979	0.0001
McGill evaluative	1.45 ± 0.51	1.42 ± 0.50	1.00 ± 0.64	1.33 ± 0.65	**0.110**	0.064
McGill 3 total dimensions	9.19 ± 3.84	9.66 ± 2.26	7.45 ± 4.37	9.19 ± 3.84	0.346	0.023
BPI %24 h	40.75 ± 33.01	45.23 ± 32.49	60.00 ± 31.95	45.23 ± 30.59	0.160	0.050
BPI worst pain	7.25 ± 2.48	7.57 ± 2.35	4.15 ± 2.60	6.28 ± 3.31	**0.035**	0.110
BPI average pain	4.50 ± 2.13	5.33 ± 2.37	2.55 ± 2.25	4.47 ± 3.09	0.090	0.072
BPI lowest pain	2.65 ± 1.95	3.80 ± 2.74	1.95 ± 2.06	3.14 ± 2.81	0.948	0.000
BPI current pain	4.55 ± 2.81	5.42 ± 3.29	2.80 ± 2.74	4.23 ± 2.89	0.510	0.011
BPI general activities	5.50 ± 3.88	4.95 ± 3.13	2.20 ± 2.62	4.66 ± 3.18	**0.002**	0.229
BPI mood	4.80 ± 3.45	4.61 ± 3.66	2.80 ± 2.21	4.38 ± 3.76	**0.037**	0.107
BPI work	4.25 ± 3.55	5.38 ± 4.21	2.95 ± 2.87	4.14 ± 3.67	0.948	0.000
BPI relationships	1.40 ± 3.16	2.38 ± 4.09	1.50 ± 3.15	2.80 ± 3.85	0.746	0.003
BPI sleep	4.65 ± 3.51	5.57 ± 3.10	2.90 ± 3.29	5.47 ± 3.58	**0.020**	0.131
BPI enjoyment of life	2.30 ± 3.65	4.42 ± 3.94	1.45 ± 2.52	4.28 ± 4.08	0.526	0.010
BPI walk	0.65 ± 1.42	1.85 ± 3.16	0.55 ± 1.82	1.57 ± 3.02	0.868	0.001
BPI total interference (sum)	23.55 ± 14.37	29.19 ± 17.73	14.35 ± 11.93	27.33 ± 19.12	**0.037**	0.106

Comparison of the effects of dry needling or sham stimulation, from day 7 to day 14, on the HAD depression and anxiety scores, the McGill questionnaire sensory, affective and evaluative scores, BPI total interference score, and its effect size. Data presented as mean ± standard deviation. *P* value for the interaction between group and time.
BPI, Brief Pain Inventory; HAD, Hospital Anxiety and depression scale.

needling were reported by 4 patients in the active group and 3 patients in sham group, with no functional impact.

3.9. Blinding assessment

At the end of the study, 45% of the participants in the active group reported they were able to tell in which group they were allocated to, and among them, 55% guessed it right. In the sham group, these proportions were 62% and 47%, respectively. When asked if the patients would like to maintain active dry needling sessions for a longer period, should this option be offered to them, affirmative answers were given by 70% of the active group and 55% of the placebo group. These proportions were not significantly different.

4. Discussion

We have shown that patients with chronic shoulder pain treated by dry needling had a significant improvement in pain intensity and pain interference with daily activities compared with sham procedure, an effect that persisted for at least 7 days. Improvements started 2 days after needling and persisted for at least 7 days thereafter. We have also described the temporal pattern of pain relief caused by DN, which started on the second and persisted until the seventh day postprocedure. The study also evaluated in a sham-controlled trial the effects of a single session of dry needling on pain intensity and explored the concomitant changes in cutaneous sensory thresholds with a battery of QST in the area of referred pain (eg, secondary hyperalgesia reduction) and its potential role in predicting the temporal persistence of the analgesic effects caused by the needle procedure.

DN analgesic effects were not limited to pain intensity, but also included positive effects of DN on pain interference with daily activities and improvement in global impressions of change. These are original information that add to a literature populated by studies devoid of sham arms[6,19,29] or providing a superficial report on the sham technique[20] such as its actual procedure, its duration, depth of needle insertion,[20] or pain intensity triggered by the sham procedure.[13,51] This last point is of significant importance because pain during sham needling may, by itself, engage nonspecific top–down pain modulatory systems and trigger pain relief that would be not specific and not related to the trigger point treatment per se, being simply the fruit of the pain suppressive effect of a stronger concomitant nociceptive stimulus.[47] Here, we took special care to control for the duration and for the intensity of both the active DN and its sham version so that the effects of these biases would be mitigated.

Interestingly, the analgesic effects of dry needling were not immediate as would have been expected in the case where its main mechanisms of action would uniquely lay on trigger point deactivation. Contrarily, our findings showed that a rather delayed response took place, commencing 2 days after the procedure, and with a positive correlation between daily pain improvement at this time point and a more pronounced pain reduction at the seventh day postprocedure. Many of the previous studies in the DN literature reported only immediate effects[34,35] of treatment, which have provided mechanistic insights into the technique in one hand, but limited clinical impact on the other. In addition, this temporal profile of analgesia installation after DN may explain some negative results based on immediate pain assessment after the procedure.[36] Considering these findings, we hypothesized that clinically meaningful pain improvement occurs after a delay of

a few days after dry needling, and it may not be detected acutely. In this line, DN has previously been reported to possess analgesic effects for painful syndromes where myofascial pain was not present, suggesting that DN analgesic effects would rely not only on the mechanical effects of needle insertion and trigger point treatment, but, instead, on the engagement of other pain suppressive mechanisms. For instance, a Cochrane systematic review of 35 randomized controlled trials evaluated the efficacy of dry needling and treatment of mechanical nonspecific low-back pain, with positive evidence of an immediate and short-term pain relief, although with a small effect size.[26] Similar findings have been reported for nonspecific shoulder pain[11] lateral epicondylitis-related pain.[53] In fact, it has been reported that DN targeting MTrPs or the adjacent muscle outside the MTrP area have similar results in poststroke shoulder pain.[33] Mechanisms of pain reduction after DN may involve both local (peripheral)[9] and central effects.[47] The local twitch response and mechanical inactivation of the trigger point may result in muscle soreness after the procedure,[50] which is detected on the day after needling. Trigger point dry needling results in local muscle microtrauma and may disrupt dysfunctional endplates[29] causing an involuntary spinal cord reflex contraction of the muscle fibers in a taut band (local twitch response), clearing the excessive buildup of acetylcholine.[10] Although the acute effects on DN over the MTrPs can be immediate, the biochemical changes responsible for the specific effects of needling[49] compared with shallow treatment by the sham procedure may take hours to days to build up. Some trials have found that deep dry needling is associated with clinically meaningful results for pain and functionality in the short-term with a single session of active and latent MTrP DN[11] and at 6 months follow-up after up to 4 sessions of DN.[12]

Growing evidence suggests that deep muscle DN per se, irrespective of its effects in MTrPs, may also decrease pain. Indeed, our results further suggested a different main mechanism driving the analgesic effects of dry needling in pain MPS relief, because the main effects occurred after 2 days of the procedure, which would not be expected it treatment of the trigger point were the sole and main responsible for its analgesic effects. We hypothesized that DN might trigger conditioned pain modulation responses, inducing analgesia by descending inhibition. Alternatively, DN may modulate pain by reducing substance P and CGRP concentrations and increasing the release of endogenous opiates, such as beta-endorphin, enkephalin, and dynorphin in nociceptive pathways, causing a decrease in hyperalgesia that would buildup in days.[10] Also, it has also been suggested that acupuncture (and possibly DN) may engage serotoninergic descending pain inhibitory pathways,[47] with effects of needling in the release of neuropeptides on serotoninergic neurons because of activation of enkephalin interneurons[14] that could not take place immediately after needling.

The dry needling procedure is very similar to the ancient "ashi" point acupuncture technique, where an acupuncture needle is inserted into the painful area, irrespective of the presence of MPS or trigger points locally. Early Chinese physicians proposed that targeting painful areas leads to a reduction in muscle tenderness. Our QST results further support the idea of the DN effect dissociated from the acute effects on MTrPs. Dry needling did lead to a significant reduction in mechanical hyperalgesia area over the painful area right after needling, which also persisted until the seventh day of follow-up. These suppressive effects in secondary hyperalgesia over referred pain area were expected and were already reported. However, these changes did not correlate with clinical pain relief. These data further suggest that acute DN effects on MTrPs and secondary hyperalgesia were independent of the procedure's long-term clinical analgesic properties. Although previous studies have suggested that DN effects in sensory thresholds would correlate with pain relief,[35] these reports were not based on a broader QST assessment. We believe our findings were due to the use of 2 control areas for QST in this study: the contralateral mirror area over the contralateral shoulder and an ipsilateral area over the trunk. We undertook the 2-control area approach based on the finding that shoulder pain is bilateral in at least 41% of patients,[7] and this would bias a solely contralateral assessment of QST abnormalities. This methodological choice probably reduced local sensory changes occurring with time and provided a more adapted and specific control area.

Considering the importance of blinding in clinical research, and that dry needling is an interventional treatment, adequate participant blinding has been challenging in interventional trials.[13] A systematic review evaluated 19 randomized controlled trials of high quality on dry needling in MSK pain in general. Only 10 (52%) included a sham intervention, and only 3 of them actually assessed the quality of blinding.[5] Our blinding assessment demonstrated that patients could not accurately tell which treatment group they were allocated into, indicating an adequate blinding. To the best of our knowledge, this was the first study to standardize, describe in detail, control for pain during the sham and active procedure, and film the needling intervention, which, we believe, was a major positive methodological improvement.

Our study had some limitations that should be considered in interpreting these results. The treatment of chronic MPS usually requires a course of treatment and not only one single intervention.[50] Also, because we stopped our assessment on the seventh day after needing, we do not know the analgesic effect's exact time duration. In addition, dry needling is rarely used as a monotherapy in clinical practice, and its effect in multimodal real-life treatment approaches remains to be determined. This randomized controlled trial demonstrated analgesic effects of local dry needling in shoulder pain for patients with chronic shoulder pain because of MPS. Our results suggest a pragmatic next step in trials on DN for pain. Because the analgesic effects persisted for at least 7 days after the procedure, this may impact the dosing of next studies proposing DN as a long-term treatment approach for MPS. One could propose that weekly DN sessions should be used instead of daily session protocols that are costly and decrease treatment compliance.

Disclosures

The authors have no conflicts of interest to declare.

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This trial was registered at Clinical Trials (#NCT02179320).

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A111, http://links.lww.com/PR9/A112.

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São Paulo, 06 de outubro de 2012.

Prof. Dr. Valdir Golin
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