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Effects of the carrier frequency of interferential current on pain modulation and central hypersensitivity in people with chronic nonspecific low back pain: A randomized placebo-controlled trial

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Abstract

Background: Interferential current (IFC) is commonly used for pain relief, but the effects of carrier frequency of the current and its action on pain mechanisms remain unclear. This randomized placebo-controlled trial tested the effects of IFC in people with chronic nonspecific low back pain.
Methods: One hundred and fifty participants were randomly allocated into three groups: 1 kHz, 4 kHz and placebo. The primary outcomes were pain intensity at rest in the first session (immediate effect of the IFC), after 12 sessions, 4 months after randomization (follow-up) and during movement (first and last session). The secondary outcomes were disability, global perceived effect, functional performance, discomfort caused by the IFC, use of analgesics and physiological measures of pain.
Results: Only during the first session, there was a significant decrease in pain intensity in the active groups. However, there were no differences in the improvement of pain at rest or during movement in the active groups compared to the placebo group in the remaining sessions. The frequency use of analgesics was significantly decreased in the active groups. For pain physiology measures, there was a significant increase in pressure pain thresholds in both active groups compared to the placebo group and a reduction in the temporal summation in the 1 kHz group compared to the other groups.
Conclusions: These results suggest that although the IFC has changed some physiological mechanisms of pain and showed decrease frequency use of pain medication, there was no change in the primary aim, pain intensity.

What does this study add?

- The interferential current (IFC) presented advantages in the physiological measures of pain and showed decrease frequency use of pain medication.
- Future studies should investigate analgesic intake with IFC treatment.

1. Introduction

Chronic low back pain is an important public health problem (Delitto et al., 2012) because it can directly affect quality of life and daily activities (Koldas Dogan et al., 2008). Low back pain is also responsible for high rates of absenteeism at work and high socioeconomic

costs worldwide (van van Tulder et al., 2006; Delitto et al., 2012). Approximately 95% of people with chronic low back pain have a nonspecific cause for their pain (Delitto et al., 1995), that may be associated with a deficiency in endogenous pain control (Peters et al., 1992; Mlekusch et al., 2013) and increased central sensitization (Giesecke et al., 2004; O'Neill et al., 2007; Staud, 2011; Mlekusch et al., 2013).

Treatments for chronic low back pain primarily aim to decrease pain and disability (DeRosa and Porterfield, 1992). Interferential current (IFC) is one of the existing electrotherapy treatments used to reduce pain and has been studied for its effectiveness in relieving low back pain (Zambito et al., 2006; Fuentes et al., 2010; Facci et al., 2011). However, there is a lack of high-quality studies assessing the effects of IFC in people with chronic low back pain (Fuentes et al., 2010). Only one study compared IFC to placebo during a single treatment session (Fuentes et al., 2014), and a systematic review on IFC for management of musculoskeletal pain concluded that more studies assessing the isolated effects of IFC are needed (Fuentes et al., 2010).

Enhanced excitability in the central nervous system is an important phenomenon observed in people with chronic low back pain (O'Neill et al., 2007; Meeus et al., 2010; Imamura et al., 2013) suggesting an amplification of nociceptive processes (Mlekusch et al., 2013). Furthermore, studies in patients with chronic pain have shown impaired conditioned pain modulation (CPM) (Peters et al., 1992; Staud et al., 2003; Pielsticker et al., 2005; Sandrini et al., 2006), including those with chronic low back pain (Peters et al., 1992). Animal studies using transcutaneous electrical nerve stimulation (TENS) show activation of central inhibitory pathways (Sluka, 1998; Kalra et al., 2001; Maeda et al., 2007; DeSantana et al., 2009) and reduced central excitability (Sluka et al., 1999, 2005; Ma and Sluka, 2001; Lisi and Sluka, 2006). One previous study showed IFC improves pressure pain threshold (PPT) after a single IFC session in people with chronic low back pain (Fuentes et al., 2014), and prior studies show TENS increases PPTs in healthy individuals and those with chronic pain (Liebano et al., 2011; Pantaleao et al., 2011; Vance et al., 2012; Dailey et al., 2013). Furthermore, TENS restored CPM in people with fibromyalgia (Dailey et al., 2013).

The physical properties of IFC and TENS are different. The active element of TENS is low-frequency pulsed currents (1–200 Hz), whereas IFC is a medium-frequency alternating current, with carrier frequencies of 1 to 10 kHz and modulated in amplitude (Pantaleao et al., 2011). Theoretically, IFC has the advantage of reducing the skin impedance, deeper penetration into tissues and is perceived as more comfortable (Pantaleao et al., 2011; Bae and Lee, 2014). Regardless of physical differences between these two types of currents, they have shown similarity in their analgesic responses (Johnson and Tabasam, 2003b; Tugay et al., 2007; Facci et al., 2011; Bae and Lee, 2014).

Optimal stimulation parameters are critical to effectiveness of electrotherapeutic modalities (Sluka and Walsh, 2003; Johnson, 2014). For IFC, the carrier frequency of the current has been suggested as an important parameter to achieve the most effective hypoalgesic response (Dounavi et al., 2012; Venancio et al., 2013). A study from our group showed that although higher IFC carrier frequencies (8 and 10 kHz) promote a more comfortable stimulation they are less effective than 1 kHz frequency for hypoalgesia in healthy control subjects (Venancio et al., 2013).

The primary objective of this study was to investigate the effects of the carrier frequency of the IFC in nonspecific low back pain. The secondary objectives were to evaluate disability, global perceived effect, functional performance, discomfort produced by IFC, use of analgesic medication and physiological measures of pain.

2. Methods

The study design was a randomized placebo-controlled trial to test the effect of IFC in people with chronic nonspecific low back pain. This trial was prospectively registered at the Brazilian Clinical Trials Registry – ReBEC, RBR-8n4hg2 and the trial protocol has been published (Correa et al., 2013). We tested effectiveness of two carrier frequencies, compared to placebo, on a variety of outcomes in response to a single application, after 12 sessions spread over 4 weeks and 4 months after randomization (follow-up, 3 months after completion of IFC treatment). Subjects were randomly allocated into three groups: 1 kHz IFC, 4 kHz IFC and placebo IFC. The evaluator and patient remained blinded to treatment. The person applying the IFC was not blinded to the treatment due to the nature of the interventions. The study was approved by the Research Ethics Committee of the Universidade Cidade de São Paulo (UNICID).

2.1 Participants

Sample size was calculated to determine the total number of study participants needed to detect a difference of 1 point for the pain intensity outcome, as

measured using the verbal numerical rating pain scale (Costa et al., 2008) with a standard deviation of 1.47 points (Werners et al., 1999). An 80% statistical power, 5% alpha and possible sample loss of 15% were considered. Thus, 50 subjects per group were needed (150 in total) (Minitab, v.15; State College, PA, USA). The estimates used in the sample size calculation were lower than the ones suggested as the minimum clinical important difference to increase the precision of the estimates of the effects of the interventions (Parreira et al., 2014). Individuals were recruited from those who sought physical therapy treatment at the UNICID clinic and Centro Especialidades Médicas de Guarulhos through advertisements in the media and through medical referral. These patients were on a waiting list to receive the treatment. Individuals of both sexes, between 18 and 80 years old were included if they presented with nonspecific low back pain for at least 3 months and had a minimum level of pain of 3 over the last 7 days on the verbal numerical rating pain scale (0–10) (Costa et al., 2008). Subjects were excluded if they had serious spinal disorders, such as fractures, tumours, or inflammatory arthritis disease; nerve root disorders confirmed by neurological tests (disc herniation and spondylolisthesis with neurological impairment, spinal canal stenosis and others); neurological diseases; severe cardiorespiratory disease; pregnancy; skin infection or lesions or change in sensation at the IFC application site; cancer; cardiac pacemaker; or allergy to electrodes. Subjects were allowed to use analgesic medications but were asked to refrain from other nonpharmacological treatments for pain during the study. If eligible, subjects were informed about the aims of the study and signed an informed consent document prior to participation in the study. They were then randomly assigned to one of three groups: 1 kHz IFC (n = 50), 4 kHz IFC (n = 50) or placebo IFC group (n = 50). Randomization was performed by a researcher who was not involved in the recruitment or treatment of participants. The subject allocation was performed randomly using the website *randomization.com*, and the group codes were kept in sequentially numbered, sealed, opaque envelopes.

2.2 Outcome measurements and follow-up

2.2.1 Primary outcomes

2.2.1.1 Pain intensity at rest. Pain intensity at rest was assessed using a verbal numerical rating pain scale (Turk, 1992) that evaluates pain intensity perceived by the patient using a 11-point pain scale (ranging from 0 to 10), where 0 is rated as 'no pain' and 10 as 'worst pain imaginable' (Costa et al., 2008). Pain intensity was assessed prior to applying the IFC, 30 min after starting IFC while the current was still on, and 20 min after turning the current off. This outcome was measured in all sessions, after 12 sessions spread over 4 weeks, and at 4 months after randomization (3 months after treatment with IFC).

2.2.1.2 Pain intensity during movement. Pain during movement was assessed during the sit-to-stand test (described below). Immediately after the test, the patient was asked to rate the back pain he/she felt during the test on the numeric rating scale. The test was performed during the first and last session just prior to applying IFC and 30 min after starting IFC while the current was still on.

2.2.2 Secondary outcomes

2.2.2.1 Functional performance. Functional performance was assessed using the sit-to-stand test. Participants were instructed to sit and stand five times from a chair with a backrest with their upper limbs crossed in front of them as quickly as possible (Simmonds et al., 1998), and time to completion was recorded. The test was performed during the first and last session just prior to applying IFC and 30 min after starting IFC.

2.2.2.2 Pressure pain threshold (PPT). PPT was measured using a digital pressure algometer (Somedic Inc., Hörby, Sweden). Two points were marked bilaterally. To assess local pain thresholds, the first point was located 5 cm lateral to the spinous process of L3 (Meeus et al., 2010) and the second was located 5 cm lateral to the spinous process of L5 (Schenk et al., 2007). To assess segmental hypersensitivity, a third point was marked over the tibialis anterior muscle of the right lower limb, 5 cm lateral to the tibial tuberosity. To measure PPT, the circular probe algometer (1 cm^2 area) was positioned perpendicular to the skin and pressed at a rate of 50 kPa/s (Liebano et al., 2011). The participants were asked to press and release a button when the sensation of pressure became a clear pain sensation. Two measurements in kPa were collected for each area with a 30-s interval between measurements. Evaluations were performed prior to applying the

current, immediately after 30 min of IFC, and 20 min after the session ended. PPTs were performed during the first and last sessions.

The evaluator performed a preliminary intra-examiner reliability study to measure PPT at the evaluation points used in the study. Ten participants who had chronic low back pain were recruited and assessed on two occasions 48 h apart. The intra-examiner reliability for measuring PPT was estimated by calculating the intraclass correlation coefficients (ICC 3.2) for the tibialis anterior muscle [0.91; 95% confidence interval (CI) 0.31–0.95] and for the lumbar muscles (0.82; 95% CI: 0.65–0.97).

2.2.2.3 Temporal summation of pain. Temporal summation was induced using an analogue pressure algometer (FPK20; Wagner Instruments, Riverside, CT, USA), which has a 0.79-cm^2 circular metallic tip. The intra-examiner reliability for measuring the temporal summation in the lumbar region was 0.89 (95% CI: 0.57–0.97). The area chosen for temporal summation analysis was the site that showed the lowest pain threshold during the low back algometry. To determine the pressure to use during temporal summation, three PPT measurements were taken in the lumbar region at the lowest pain threshold point. The average of the three measurements was used as the pressure value for temporal summation. Ten stimuli were then applied with the algometer in the respective region. Each stimulus was maintained for 1-s with a 1-s inter-stimulus interval. The participants were instructed to report pain intensity through the verbal numerical pain rating scale during the first, fifth and tenth stimulus (Cathcart et al., 2009). Difference scores were calculated as the pain rating of the 10th pulse in the train minus the pain rating of the first pulse in the train. Thus, these scores represented the magnitude of temporal summation at lumbar area. Evaluations were performed prior to applying IFC, after 30 min IFC while the stimulation was still on, and 20 min after removing IFC for both the first and last sessions. To avoid the interference of sensitization in the PPT evaluation performed previously, temporal summation evaluation was started 2 min after PPT evaluation.

2.2.2.4 Conditioned pain modulation (CPM). The integrity of the descending inhibitory systems was tested using a CPM test (Knudsen and Drummond, 2009). The conditioned stimulus was the immersion of the lower limb into an ice water bath on the side ipsilateral to the most painful low back region. In the case of bilateral pain, the subject was instructed to report the more painful side (Neziri et al., 2012). If there was no consensus on which side was the most painful, the right leg was used. The leg was immersed in a 4 °C ice water bath 3 cm above the lateral malleolus of the ankle. PPT was recorded in the lower back 30 s after immersion. The intensity of CPM was assessed by calculating the PPT difference scores (variation from pre-immersion values), where positive values represent hypoalgesia and negative values represent hyperalgesia. The CPM test was performed on the first day of treatment before IFC and on the last day of the session prior to applying IFC.

2.2.2.5 Disability. Disability was assessed using the Roland Morris disability questionnaire, which is widely used to evaluate the functional performance associated with low back pain (Roland and Morris, 1983; Nusbaum et al., 2001). It consists of 24 items that describe situations of daily activities that people have difficulty performing due to low back pain. The questionnaire was administered on the first day of treatment, at the last session and at the 4 month follow-up phone interview.

2.2.2.6 Global perceived effect. The global perceived effect was assessed using the Global Perceived Effect Scale (Feinstein, 1987; Costa et al., 2008; Willemink et al., 2012). The scale has 11 points, which vary from −5 points (vastly worse), 0 (unchanged) to +5 (completely recovered). Participants were asked the following question: 'Compared to when this episode first started, how would you describe your back these days?' The scale was administered before and after the 12 treatment sessions, and at the 4-month follow-up by phone interview.

2.2.2.7 Discomfort caused by IFC. Discomfort caused by IFC was assessed using a 10-cm visual analogue scale (VAS) where the far left end indicated 'very comfortable' and the far right end indicated 'very uncomfortable' (Venancio et al., 2013). The assessment of discomfort was performed 30 min after starting IFC in all the sessions.

2.2.2.8 Use of analgesic medications. All subjects were asked to refrain from pain medications 24 h prior to the first evaluation. To determine the frequency use of analgesic medication, the evaluator completed a

medication recall every day during each treatment session. Participants reported opioid derivatives, muscle relaxants, acetaminophen and nonsteroidal anti-inflammatory medications taken regularly. From the second session on, participants were asked the question: 'How many times have you taken pain medications since your last treatment session?' The analysis of the frequency use of medication was performed to verify differences between-within groups over the 12 treatment sessions.

2.2.2.9 Assessment of study blinding. At the end of treatment, after the follow-up evaluations, the person applying IFC asked the evaluator if she thought the subject received active IFC or placebo IFC. The study participants also answered the same questions (Rakel et al., 2010).

2.2.2.10 Interventions. The study used a randomized placebo-controlled trial design for the three interventions: 1 kHz IFC, 4 kHz IFC and placebo IFC. Participants received all their IFC treatments at the university physical therapy clinic three times per week on alternate days for 4 weeks. All the participants received 30 min of either active IFC or placebo IFC (the current was turned off for placebo IFC). IFC was applied using medium-frequency alternating currents (Neurovector; Indústria Brasileira de Equipamentos Médicos (IBRAMED)®). The IFC stimulator was modified particularly for this study by adding the carrier frequency of 1 kHz to the device. Subjects were placed in prone position. Two of the four 5 × 9 cm electrodes were placed 5 cm from the spinous process of L3 and L5 on one side, and another two were placed 5 cm from the spinous process of L3 and L5 on the other side. IFC was applied using the pre-modulated bipolar mode. The following parameters were used: the current carrier frequency based on the study group (1 or 4 kHz); AMF = 100 Hz; sweep frequency = 50 Hz; swing pattern = 1:1 and 30 min of stimulation. The placebo IFC group received identical procedures as the other two active groups, but the current amplitude was not increased. The patient was told that he/she may or may not feel any sensation at the application site of the electrodes (Dounavi et al., 2012). For the active groups, the therapist increased the current amplitude until the participant reported feeling a strong, but comfortable tingling sensation. Every 5 min, the therapist asked the participant if he/she still felt the 'strong, but comfortable tingling' sensation. In cases where sensation to the current decreased, the current amplitude was increased until the participant reported having the same sensation as stated earlier (Pantaleao et al., 2011; Dailey et al., 2013). In the placebo IFC group, participants were asked every 5 min if they were comfortable. To ensure that the evaluator and patient remained blinded throughout the entire process, the equipment was covered with a dark cloth. Furthermore, evaluator was not present when those questions were asked to participants.

2.3 Study procedures

The timeline for the study procedures is shown in Fig. 1. All the tests were performed with the same equipment by the same evaluator. Screening was performed, and participants who signed an informed consent were included in the study. First, the participants completed a demographic questionnaire. The order of the following evaluations was the same for all participants: use of analgesics, resting pain, disability, global perceived effect, PPT, temporal summation, CPM, functional performance and pain during movement. After evaluation, participants were randomized and categorized into the active IFC groups or placebo IFC group. Thirty minutes after starting IFC, pain at rest and during movement, discomfort caused by IFC, PPT and temporal summation was assessed during IFC. IFC was then turned off, and 20 min later pain intensity at rest, PPT and temporal summation were reassessed. During the 4-month follow-up phone interview, pain intensity, disability and global perceived effect were evaluated.

2.4 Statistical analysis

Data analysis was performed by a statistician who was blinded to treatment groups. All the statistical procedures were performed following intention-to-treat principles. Descriptive statistics of the variables were initially used for the study. The normality of the data was analysed by visually inspecting the histograms. Differences between groups for the primary and secondary outcome measurements were compared using linear mixed models (random intercepts and fixed coefficients), which incorporated terms for treatment, time and the treatment by time interactions, followed by calculation of effect size (Cohen's *d*). The coefficients of the treatment by time interactions provided estimates of the effects of the intervention (from estimated marginal means command on SPSS). We decided to use linear mixed models due to the following reasons: 1) This type of analysis

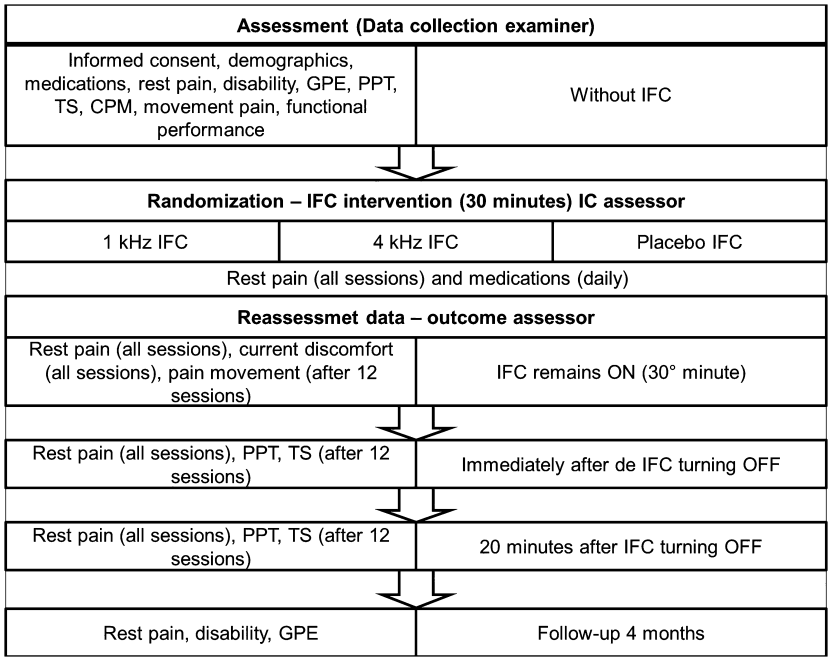

Figure 1 Session order with randomization of IFC treatment. GPE = global perceived effect, PPT = pressure pain threshold, TS = temporal summation, CPM= conditioned pain modulation.

automatically adjusts the treatment effects for the dependency of multiple time points estimates (we did not adjusted the analysis for any other variables), 2) It uses all data from all time points to calculate each treatment estimate and 3) Deals optimally with missing data by predicting the best value for patients who were not possible to be followed up (Twisk, 2004). For the analysis of study blinding, a chi-squared test was used. A between-within groups ANOVA and Tukey's post hoc test were used to compare the number of times that participants had to take medication over the course of the treatment. The Statistical Package for the Social Sciences for Windows version 19.0 and Microsoft Excel 2007 were used for the data analysis. All tests were performed assuming a significance level of $p < 0.05$.

3. Results

The study was conducted at the Physical Therapy Clinic of the Universidade Cidade de São Paulo and at the Centro de Especialidades Médicas de Guarulhos, Brazil, between October 2012 and June 2013. The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Fig. 2. Table 1 shows the demographic data and baseline values for each measurement for individual study groups. Most of the participants were women and routinely used analgesic medications to relieve low back pain. The mean duration of low back pain of the study participants was greater than 8 years, and mean pain intensity over the last week was higher than 7 points on the pain scale. None of the participants crossed over groups during the study.

3.1 Pain intensity at rest

The mean resting pain intensity (scale of 0 to 10) at baseline was similar among the three groups. Pain intensity significantly decreased in all three groups by 3–4 points on a 0–10 scale. However, after 12 treatment sessions, there was no statistically significant difference among groups (Table 2). In the first session (immediate effect of IFC), there was a significant difference in pain intensity 20 min after turning off the current in the 1 kHz IFC and 4 kHz IFC groups compared with the placebo IFC group (Table 3). At the 4-month follow-up, there was no difference between the groups (Table 2). When comparing pain intensity assessed at each treatment session, the IFC 1 kHz group showed significant improvement in pain intensity within 30 min of turning the current on compared to the placebo group only after the first treatment session. The IFC 4 kHz group presented differences in pain intensity compared to placebo group only on the 12th session, 20 min after turning off the

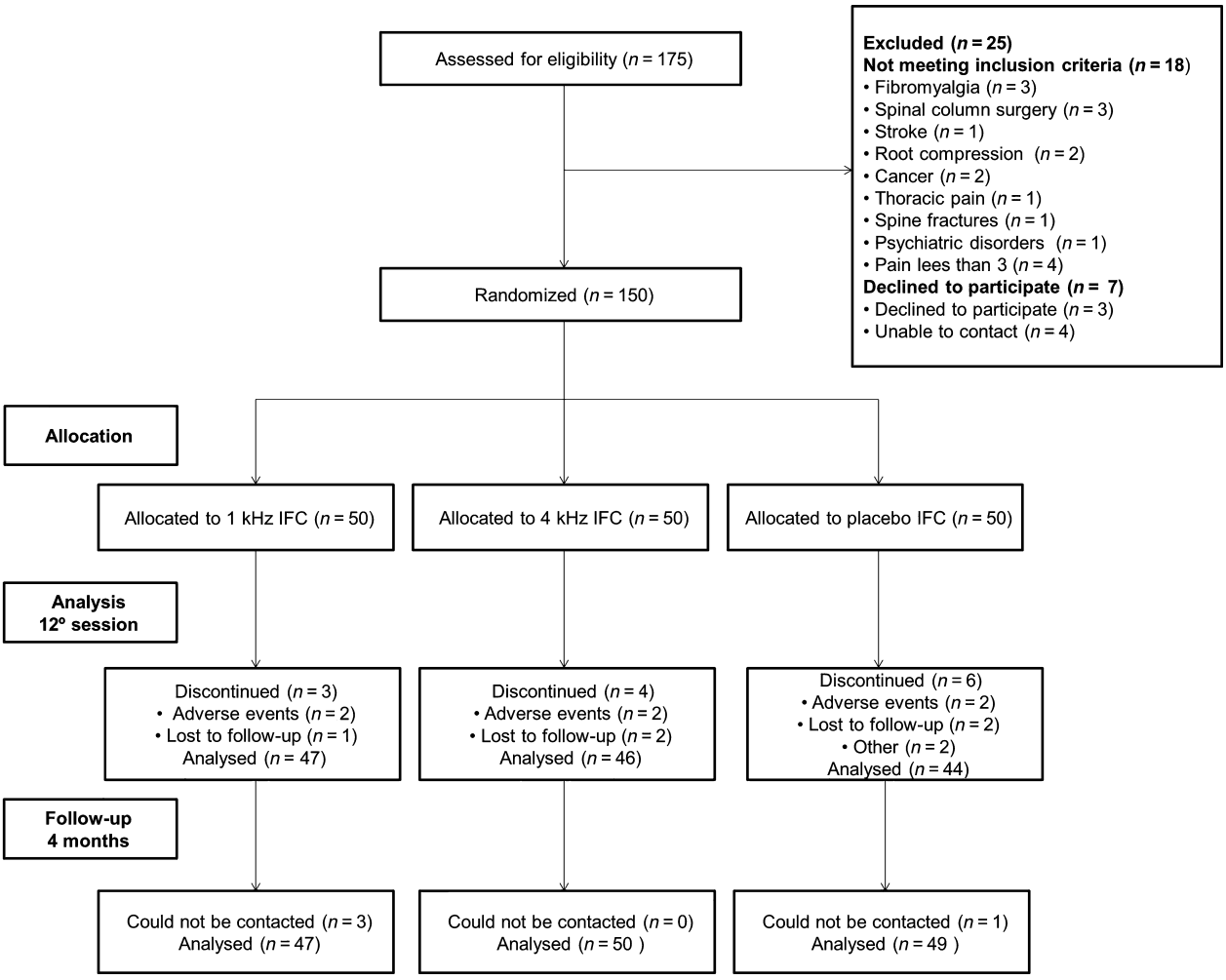

Figure 2 Consort diagram for the study.

current. There was no difference between groups in the remaining days of treatment.

3.2 Pain during movement and functional performance

The pain intensity and the time to perform the sit-to-stand test decreased in all three groups. However, after 12 treatment sessions, there was no significant difference between the groups in pain intensity during the sit-to-stand test or the sit-to-stand time (Table 2).

3.3 Disability

Despite the improvement of disability in all groups, there was no difference between the groups when comparing improvements in disability at the end of treatment. At the 4-month follow-up, there was also no statistically significant difference between the groups (Table 2).

3.4 Global perceived effect

Difference in global perceived effect was observed in all groups. However, there was no difference between the groups after 12 treatment sessions or at the 4-month follow-up contact (Table 2).

3.5 Use of medication

After treatment, the groups were compared for the number of times that participants took analgesic and/or anti-inflammatory medication over the course of the treatment. Statistical analyses of the number of times patients needed to take pain medication using between-within groups ANOVA showed significant differences: over time ($p < 0.0001$); interactive effect between time and group ($p < 0.027$) and between groups ($p = 0.004$). The 1 and 4 kHz IFC groups showed a statistically significant decrease in the total frequency use of pain medication

Table 1 Demographics and clinical characteristics at baseline.

Variable	Placebo IFC group (n = 50)	1 kHz IFC group (n = 50)	4 kHz IFC group (n = 50)
Demographic characteristic			
Age (yr), mean (SD)	49.4 (11.6)	50.5 (13.1)	53.6 (11.5)
Female, n (% sample)	40 (80)	35 (70)	40 (80)
Education, n (% sample)			
School certificate	19 (38)	18 (36)	21 (42)
High school	22 (44)	22 (44)	23 (46)
Some college	8 (16)	8 (16)	6 (12)
Other (higher than college)	1 (2)	2 (4)	–
Body mass index (kg/m^2), mean (SD)	27.9 (4.3)	26.5 (3.9)	28.5 (5.3)
Pain during last 7 days (0–10 scale), mean (SD)	7.4 (1.7)	7.5 (1.7)	7.5 (1.5)
Low back pain duration (mo), mean (SD)	96.3 (100.3)	95.3 (101.1)	99.4 (102.6)

compared with the placebo group. There was no difference between the 1 and 4 kHz IFC groups for the frequency use of pain medication (Table 4).

3.6 Pressure pain threshold

There was a statistically significant increase in PPT in both the low back region and tibialis anterior muscle, but only for the 1 kHz group compared with the placebo group after 12 treatment sessions (Table 2). There was no difference in the local (low back) or segmental (tibialis anterior) PPT between the 1 and 4 kHz groups (Table 2). In the first session for the low back PPT (local sensitization) there was a significant increase for the 1 and 4 kHz groups compared to the placebo group. Moreover, the 1 kHz group showed a greater local hypoalgesia when compared to the 4 kHz group. For the tibialis anterior PPT (segmental sensitization), there was a significant increase for the 1 kHz group compared to the placebo group (Table 3).

3.7 Temporal summation of pain

There was a statistically significant decrease in the 1 kHz IFC group compared to the placebo IFC group and 4 kHz IFC group (Table 2). In the first session, the temporal summation only showed a significant difference for the 4 kHz group compared to the placebo group 20 min after turning off IFC (Table 3).

3.8 Conditioned pain modulation

There was an increase in PPT in all three groups in the low back region during the cold pressor test, indicating activation of the conditioned pain modulation system after the active and placebo IFC sessions. However, these data were not statistically significant between groups (Table 2).

3.9 Discomfort caused by the current

There was no difference in the active 1 kHz (2.4 ± 0.3 cm, mean $\pm$ SD) or 4 kHz (2.0 ± 0.2 cm, mean $\pm$ SD) groups for discomfort caused by the IFC ($p > 0.05$).

3.10 Study blinding

All the participants were asked at the 4-month follow-up which group (placebo or active) they thought they were in. In the active group, 83.5% of participants were correct, and 16.5% misidentified their allocation group ($p = 0.0001$); however, in the placebo group, 46% were correct, and 54% misidentified their allocation group ($p = 0.88$). At the end of follow-up, the evaluator also answered the same question concerning which group the subjects were included in, she was correct for 40% of the group allocations ($p = 0.30$). This result indicates that the evaluator and subjects in the placebo group were appropriately blinded, but it also demonstrated the difficulty of blinding the subjects in the active group. It is difficult to achieve complete blinding of patients in electrotherapeutic studies, particularly when the stimulus is applied at adequate intensities (Deyo et al., 1990). Indeed prior studies show that it is possible to adequately blind placebo treatments with electrotherapeutic modalities, but not active treatments (Deyo et al., 1990; Rakel et al., 2010).

4. Discussion

This study shows that treatment with active IFC was not better than placebo IFC, neither after 12 treatment sessions nor 4 months after randomization. However, there were changes in physiological measures of pain in the 1 kHz group compared to the placebo group. Interestingly, we show there was significant improvement in pain intensity at rest for the immediate effects of the IFC (single session) in the active groups compared to the placebo group, corroborating a previous study (Fuentes et al., 2014). The results in physiological measures of pain and improvement in pain intensity at rest had small or moderate effect sizes. A previous review showed that treatment with TENS for chronic low back pain has small effect sizes (Keller et al., 2007). Pain intensity

Table 2 Mean (SD) for continuous outcomes at all study visits for each group, adjusted mean difference (95% CI) between groups and effect sizes (Cohen's *d*).

	Adjusted Mean Difference (95%CI)								
Variable	Placebo $\bar{x}$ (SD)	1 kHz $\bar{x}$ (SD)	4 kHz $\bar{x}$ (SD)	1 kHz vs Placebo (95% CI)	Cohen's *d*	4 kHz vs Placebo (95% CI)	Cohen's *d*	1 kHz vs 4 kHz (95% CI)	Cohen's *d*
Pain at rest (0–10)									
Baseline	6.2 (2.0)	6.3 (2.1)	6.2 (2.0)	–		–		–	
12 sessions	3.1 (2.4)	2.1 (2.1)	2.2 (2.2)	0.9 (2.0 to 0.2)	0.4	0.8 (0.3 to 1.9)	0.4	0.01 (1.1 to 1.0)	0.05
4 months	4.7 (3.3)	4.6 (2.9)	4.4 (2.7)	0.4 (1.0 to 1.1)	0.03	0.2 (0.9 to 1.2)	0.1	- 0.6 (0.8 to 1.3)	0.07
Pain with movement (0–10)									
Baseline	4.4 (2.9)	4.8 (3.0)	4.4 (2.9)	–		–		–	
12 sessions	1.8 (2.3)	0.9 (2.8)	1.4 (1.8)	1.0 (2.2 to 0.2)	0.3	0.2 (1.0 to 1.4)	0.2	0.7 (1.9 to 0.5)	0.2
Functional performance(s)									
Baseline	17.3 (9.0)	14.5 (6.5)	15.8 (5.6)	–		–		–	
12 sessions	12.0 (4.8)	9.6 (3.3)	11.0 (3.5)	0.3 (2.2 to 2.8)	0.6	0.8 (2.8 to 2.2)	0.2	0.0 (2.4 to 2.4)	0.4
Disability (0–24)									
Baseline	15.1 (6.0)	13.3 (4.9)	14.2 (5.5)	–		–		–	
12 sessions	10.9 (7.3)	8.1 (6.7)	7.6 (6.7)	0.8 (3.1 to 1.5)	0.4	2.1 (0.2 to 4.5)	0.5	1.3 (1.0 to 3.7)	0.07
4 months	10.3 (8.3)	9.0 (7.0)	9.3 (7.0)	0.3 (2.0 to 2.6)	0.2	0.2 (2.1 to 2.5)	0.1	0.5 (1.8 to 2.8)	0.04
GPE (5/+5)									
Baseline	2.5 (2.8)	1.5 (3.2)	2.5 (2.7)	–		–		–	
12 sessions	2.6 (2.1)	3.5 (1.9)	3.5 (1.8)	0.0 (1.4 to 1.4)	0.4	1.1 (2.5 to 0.3)	0.5	1.1 (2.6 to 0.3)	0.0
4 months	1.6 (3.1)	1.7 (3.1)	1.8 (3.0)	0.6 (2.0 to 0.7)	0.03	0.5 (1.9 to 0.9)	0.06	1.1 (2.5 to 0.3)	0.03
Lumbar PPT (kPa)									
Baseline	264.4 (82.7)	241.4 (90.3)	253.5 (104.0)	–		–		–	
12 sessions	252.8 (79.9)	297.7 (130.0)	279.7 (103.4)	57.5 (0.0 to 115.0)[a]	0.4	24.2 (81.9 to 33.49)	0.5	33.3 (24.4 to 91.0)	0.0
Anterior tibialis PPT (kPa)									
Baseline	303.0 (91.7)	256.5 (87.0)	267.7 (109.2)	–		–		–	
12 sessions	302.6 (91.1)	322.8 (138.2)	303.0 (105.7)	60.1 (14.6 to 105.6)[a]	0.2	28.7 (74.5 to 17.1)	0.0	31.3 (13.9 to 76.6)	0.2
Temporal Summation (0–10)									
Baseline	2.3 (2.0)	2.0 (1.5)	2.4 (1.7)	–		–		–	
12 sessions	1.4 (2.0)	0.6 (1.3)	1.5 (1.9)	1.0 (0.0 to 1.9)[a]	0.5	0.0 (0,9 to 1.0)	0.05	1.0 (1.0 to 1.9)[b]	0.6
CPM (kPa)									
Baseline	46.2 (56.1)	24.8 (67.6)	32.8 (57.5)	–		–		–	
12 sessions	26.7 (50.3)	40.5 (82.4)	51.8 (78.6)	4.4 (36.5 to 27.7)	0.2	16.9 (49.2 to 15.3)	0.4	21.3 (53.5 to 10.9)	0.1

95% CI = 95% confidence interval, GPE = global perceived effect, PPT = pressure pain threshold, TS = temporal summation, CPM = conditioned pain modulation. The variable marked in grey represents the primary outcome, and other variables are secondary outcomes. Positive values indicate improvements in the outcomes of pain, disability, global perceived effect, pressure pain threshold, conditioned pain modulation and the functional performance.

[a]Significant difference compared to the placebo group.

[b]Significant difference between the 1 kHz group and 4 kHz group, $p < 0.05$ considered significant.

Treatment estimates were adjusted for baseline and previous time points (e.g. data from 4 months were adjusted for the data from after treatment and baseline).

Table 3 Effects of intervention at IFC 30 min ON and 20 min after IFC OFF [adjusted mean difference score between groups – with 95% confidence interval and effect sizes (Cohen's *d*)] in the first session.

Variable	1 kHz vs Placebo (n = 50)	Cohen's*d*	4 kHz vs Placebo (n = 50)	Cohen's*d*	1 kHz vs 4 kHz (n = 50)	Cohen's *d*
Pain at rest (0–10)						
30 min	0.2 (−0.7 to 1.1)	0.06	0.2 (−0.7 to 1.0)	0.09	0.4 (−0.5 to 1.2)	0.1
50 min	0.9 (−1.7 to −0.0)*	0.4	1.0 (0.1 to 1.8)*	0.5	0.1 (−0.8 to 0.9)	0.02
Pain with movement (0–10)						
30 min	0.7 (−1.8 to 0.4)	0.2	0.5 (−0.6 to 1.6)	0.04	0.2 (−1.3 to 0.9)	0.1
Functional performance (s)						
30 min	1.0 (−0.8 to 2.8)	0.2	−0.5 (−2.2 to 1.3)	0.3	0.5 (−1.2 to 2.3)	0.1
Lumbar PPT (kPa)						
30 min	77.7 (49.3 to 106.1)*	0.7	42.5 (−70.9 to −14.1)*	0.4	35.3 (6.9 to 3.7)*	0.2
50 min	54.7 (26.3 to 83.1)*	0.4	19.0 (−47.4 to 9.4)	0.2	35.7 (7.3 to 64.1)*	0.2
Anterior tibialis PPT (kPa)						
30 min	39.2 (6.0 to 72.4)*	0.1	20.3 (−54.6 to 13.0)	0.05	18.9 (−14.4 to 52.2)	0.2
50 min	34.6 (1.5 to 67.8)*	0.0	25.1 (−58.4 to 8.2)	0.0	9.5 (−23.7 to 42.9)	0.0
TS (0–10)						
30 min	0.3 (0.5 to 1.0)*	0.07	0.4 (−0.3 to 1.2)	0.2	0.7 (−0.0 to 1.5)*	0.2
50 min	0.5 (−0.2 to 1.3)	0.1	0.4 (−0.4 to 1.2)	0.1	0.9 (0.1 to 1.7)*	0.4

PPT = pressure pain threshold. TS = temporal summation. The variable marked in grey represents the primary outcome, and other variables are secondary outcomes. Positive values indicate improvements in the outcomes of pain, functional performance, pressure pain threshold and temporal summation.

*Significant difference between the groups analysed, $p < 0.05$ considered significant.

Table 4 Number of times that patients needed to take pain medication since last treatment session.

Variable	Placebo	1 kHz	4 kHz
Treatment session			
2	23	20	17
3	21	16	7
4	25	18	17
5	39	9	22
6	41	14	20
7	56	20	18
8	42	12	19
9	42	12	14
10	43	12	10
11	20	13	9
12	16	4	4
$\bar{x}$(SD)	30.7 (15.2)	12.5 (6.0)*	13.1 (6.9)**
	Effect size (Cohen's *d*)		
	1 kHz vs Placebo	4 kHz vs Placebo	1 kHz vs 4 kHz
	1.6	1.5	0.1

*Significantly different when compared to the placebo group, $p = 0.01$.

**Significantly different when compared to the placebo group. $p = 0.014$.

during movement did not differ between the groups. Although two previous studies (Facci et al., 2011; Lara-Palomo et al., 2013) show reduced pain intensity with IFC in chronic low back pain, neither of these studies used a placebo or compared different carrier frequencies.

4.1 Pain intensity at rest

To date, three randomized controlled trials have evaluated the use of IFC in people with chronic low back pain (Facci et al., 2011; Lara-Palomo et al., 2013; Fuentes et al., 2014). Facci et al. (Facci et al., 2011), showed that both 4 kHz IFC and TENS reduced pain and disability (10 sessions, 30 min stimulation) when compared with a group received home-based guidelines. Lara-Palomo et al. (Lara-Palomo et al., 2013) showed reduced pain intensity with the combined use of 4 kHz IFC and superficial massage compared to the superficial massage only (20 treatment sessions, 30 min stimulation). The third study (Fuentes et al., 2014) showed improvements in pain intensity in the group using 4 kHz IFC (30 min stimulation) combined with enhanced therapeutic alliance. Our results similarly show an immediate effect of IFC on pain intensity when compared with placebo. IFC with lower carrier frequencies (1 kHz) was more effective than IFC with higher carrier frequencies (8 kHz and 10 kHz) for hypoalgesia in healthy subjects (Venancio et al., 2013), which may be explained on the basis of the decrease in summation and reduction in multiple nerve firing (Johnson and Tabasam, 2003a; Ward and Oliver, 2007). In this study, we choose to compare the lowest carrier frequency (1 kHz) with the most commonly used frequency for analgesia (4 kHz). We expected that the frequency of 1 kHz could have a better therapeutic

effect compared to 4 kHz. However, there was no difference between the carrier frequencies in immediate effect for the pain intensity in this study.

We show a significant improvement in resting pain in active and placebo IFC groups without a difference between groups, suggesting pain intensity is strongly influenced by placebo (Vance et al., 2012; Dailey et al., 2013). Placebo-induced analgesia is a strong modulator of central neuron activity altering neuronal activity in the areas of the brain associated with pain processing (Benedetti, 2014), and promoting release of endogenous opioids to produce analgesia (Amanzio and Benedetti, 1999). It is also possible that the lack of differences between active and placebo IFC are accounted for by the greater use of medication in the placebo group. Alternatively, passage of time, or a regression to the mean may have influenced the improvement in the placebo group.

4.2 Pain during movement and functional performance

There were no differences in pain during movement or in function between active groups compared with placebo. Previous studies show reduced movement pain with TENS (Rakel and Frantz, 2003). However, a recent study using TENS showed no difference in movement pain compared to placebo using the timed up and go test for people with knee osteoarthritis (Vance et al., 2012). Surprisingly, this study showed a reduction in pain intensity during the sit to stand test when compared to resting pain, suggesting that movement itself reduced, instead of increased, pain. Thus, the sit-to-stand test may not be an adequate test to produce movement pain in people with low back pain.

4.3 Disability

Previous studies using IFC for acute and chronic low back pain show reduced disability compared with controls (Werners et al., 1999; Hurley et al., 2004; Facci et al., 2011; Lara-Palomo et al., 2013). However, these studies used IFC in combination with other interventions and none of these studies compared IFC with placebo. In this study, there were no differences between the groups in disability. Passive treatments used alone are not expected to improve disability (Airaksinen et al., 2006; Buchmuller et al., 2012).

4.4 Global perceived effect

Since both active and placebo IFC showed similar reduction in pain, the lack of change in the global perceived effect may reflect this decreased intensity, and thus result from the effects of placebo on pain (Goats, 1990; Dounavi et al., 2012; Fuentes et al., 2014).

4.5 Pain physiology measures

In people with low back pain, lower pain thresholds were observed in areas distant from the site of pain (Banic et al., 2004). This study showed that the 1 kHz group had a significant increase in the local PPT (lumbar) and segmental PPT (tibialis anterior) compared to the placebo group, which is consistent with previous IFC study on people with low back pain (Fuentes et al., 2014). Clinically, this increase in PPT may suggest that subjects are less tender to palpation and these effects may serve as a useful measure of neuron excitability (Vance et al., 2012).

The TS protocol used in this study is thought to reflect the sensitivity of neurons in the central nervous system (CNS) to noxious stimuli (Woolf and Salter, 2000; Sarlani and Greenspan, 2002). In this study, the 1 kHz group significantly reduced TS compared to the placebo and 4 kHz group, suggesting that IFC decreased CNS sensitivity. Compared to 4 kHz, 1 kHz would result in a lower number of action potentials of the primary afferent fibres activated within each burst of IFC, resulting in less synapse fatigue (Johnson and Tabasam, 2003a; Ward and Oliver, 2007).

In this study, pain intensity, function and global perceived effect were unchanged compared to placebo. Previous research has shown that a cognitive-behavioural approach (e.g. education on the neurophysiology of pain) may play an important role in the treatment of chronic low back pain (Moseley, 2004; Moseley et al., 2004; Walti et al., 2015). Moreover, exercise, with and without pain physiology education are effective in people with low back pain (Moseley, 2004, 2005; Moseley et al., 2004; Nijs et al., 2014). Thus, IFC alone may not be sufficient to change global ratings of pain, function and disability.

No differences were observed in the active groups compared with the placebo group during the CPM test. Prior to application of IFC, there was not the expected increase in PPT normally observed in healthy controls (Mlekusch et al., 2013), suggesting that people with low back pain have inefficient CPM. However, after treatment, all groups showed an increase in PPT during CPM after 12 sessions, suggesting there was a reactivation of the endogenous descending pain modulation systems. This is in contrast to our prior study that showed an increase in the PPT during CPM in people with fibromyalgia

in a single session of TENS compared with placebo (Dailey et al., 2013), suggesting a restoration of CPM by electrotherapeutic modalities. However, in the prior study the CPM test was performed with TENS on, whereas in this study we performed the CPM test without IFC on. Thus, electrotherapeutic modalities could have a transient effect on CPM. Since both CPM (DeSantana et al., 2008, 2009) and placebo (Amanzio and Benedetti, 1999) analgesia activate endogenous opioid analgesic mechanisms, it is possible that activation of the placebo effect in this study re-engaged the CPM pathways (Amanzio and Benedetti, 1999), thus accounting for a lack of difference between active and placebo IFC groups.

4.6 Use of pain medication

There was a significant decrease in the frequency use of pain medication in the active groups compared with the placebo group at the end of treatment. Two prior studies also reported a decrease in pain medication use after IFC or TENS sessions in patients with chronic nonspecific low back pain (Facci et al., 2011) and osteoarthritis (Atamaz et al., 2012), respectively.

4.7 Internal and external validity

This study was performed in a physical therapy clinic of a Brazilian university, and the results of this study should be generalizable to groups of patients with similar characteristics. The IFC intervention implemented in our study was well defined, and we are confident that physical therapists with appropriate training would be able to perform this intervention. The systematic review of the efficacy of IFC in chronic pain concluded that there is uncertainty in effectiveness because of methodological concerns and small number of existing trials (Fuentes et al., 2010). Our trial avoided the main methodological problems of previous trials by using a placebo control group, blinding assessors and adequate power.

4.8 Study limitations

Only the evaluator and subjects in the placebo IFC group were adequately blinded to the group allocation. It is well-known that trials that subjects unblinded are more prone to bias compared to trials that were successful in blinding their patients (Hrobjartsson et al., 2014). Therefore, we must not disregard the possibility of the blinding failure on the active groups have interfered on the positive results of the study, and we strongly recommend caution while interpreting the immediate results (Table 3) of our trial due to this limitation. This study showed no difference between placebo and active IFC for our primary aim, pain, but a reduction in analgesic input, a secondary aim. This suggests that future studies should investigate analgesic intake with IFC treatment in a more comprehensive manner than this study.

In summary, there was no difference between active IFC and placebo IFC in our primary outcome measure, resting (except on the first session) and during movement pain intensity after treatment. However, when compared with placebo IFC, subjects receiving 1 kHz had greater local and segmental pain thresholds, and reduced temporal summation, though with small or medium effect sizes. Furthermore, subjects allocated to the active groups decreased only the use frequency of analgesic medications during the treatment period with high effect sizes when compared to placebo group.

Authors' contributions

JBC provided data collection and wrote the manuscript. JBC, NOTB and WPL provided data collection. REL provided concept/idea/research design and data analysis. REL, LOPC and KAS provided concept/idea/research design. REL and LOPC are the study coordinators. All authors discussed the results and commented on the manuscript and approved the final version of the study to be published.

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